ANNUAL REPORT
OF
PROGRAM ACTIVITIES
NATIONAL INSTITUTE OF DENTAL RESEARCH
Fiscal Year 1975

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service National Institutes of Health

US NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

1975

PART I	Office of the Director, Research Projects and Indexes
PART II	National Caries Program
PART III	Extramural Programs
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PART I

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

OFFICE OF THE DIRECTOR

RESEARCH PROJECTS AND INDEXES

July 1, 1974 - June 30, 1975

Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

Preface

Progress in scientific research is often so subtle that it escapes notice--and the achievements of those individuals who support that research are even less obvious. Only when dramatic discoveries are announced do the contributors to that effort gain some bit of recognition. Still, on a day-to-day basis many dedicated people are working diligently toward that eventual break-through. The annual report at NIH provides each participant in the organizational research effort with an opportunity to reflect on, evaluate, and document their contribution to science on an annual basis. This NIDR Annual Report is a record of our Institutes' activities and progress during fiscal year 1975.

For convenience in compilation and distribution, the Report is prepared in five volumes; Part I, Office of the Director and Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Collaborative Research Projects. This is the fourth year that we have combined the individual project report with the SSIE Notice of Research Project form (PHS 166) and find it most effective for our needs. These are printed on blue paper as a separate section of Volume I.

The numbering system has been changed slightly this year to conform with the NIH-wide practice for numbering grants and contracts. All intramural research projects will bear the same number during their life time and will have a "Z01" prefix. The two digits immediately following the five-digit number indicate the number of years that the project, or some identifiable portion of that project, has been active.

It should be pointed out that while the NIDR Annual Report is not a restricted document, it was prepared for administrative use at NIH and not for public distribution. No attempt has been made to evaluate the quality of research--this has been done by study sections, advisory groups or laboratory and branch chiefs--and the comments of the various contributors to this document are their own.

Recipients of this Report are encouraged to familiarize themselves with the Contents and Indexes and constructive criticism aimed at its overall improvement will be welcomed.

Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

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REPORT OF THE DIRECTOR

THE NATIONAL INSTITUTE OF DENTAL RESEARCH

July 1, 1974 - June 30, 1975

by

Seymour J. Kreshover

The National Institute of Dental Research is the only component of the NIH that addresses itself to the compelling oral health needs of the Nation and that has a unique link with a total health profession incorporating research, education and practice.

The fundamental research conducted by NIDR has achieved international as well as national acclaim in the total biomedical community. For example, the Institute is without peer in its studies of collagen, as well as in its programs of microbiology, immunology and virology. Equally significant is the contribution of intramural research to the base of biomedical knowledge with implications for diseases and disorders quite beyond the immediate consideration of the oral cavity. Thus, the role of collagenase in various skeletal, neuromuscular and skin diseases; the immune response in rheumatoid arthritis; and viral aspects of diabetes, constitute significant aspects of NIDR research. The consequent recognition by the scientific community of the accomplishments of the NIDR was evident during the past year in the large number of honors and awards conferred on staff members.

As a vital underpinning of its broad and varied research activity, major component leaders (i.e., the Associate Directors for Extramural Programs, National Caries Program and Office of Collaborative Research, as well as the Director of Intramural Research, the Clinical Director, the Scientific and Health Reports Officer and the Executive Officer) continued to serve as a planning and strategy board for both short and long-range programming.

To further strengthen the programs of the Institute, a Soft Tissue Stomatology and Nutrition Program was recently established within the Extramural Programs. The change was effected by removing this field of research from the Periodontal and Soft Tissue Diseases Program area.

Within the Intramural Programs of NIDR, two significant organizational changes were made during FY 1975. One was establishment of a Microbal Systematics Unit to collect and code microorganisms of particular interest to oral research, and the second was establishment of a Microbiology Section. Both activities are located in the Laboratory of Microbiology and Immunology.

Also during FY 1975, the NIDR implemented demonstration and control programs in its National Caries Program, having already established the safety and efficacy of several preventive measures.

In all Institute activities over the year, equal employment opportunity continued to receive high priority attention. As one essential resource for this effort, an Affirmative Action Plan Task Force was selected to develop a viable plan for the Institute.

As the Institute continues to provide evaluation and assessment of its own ongoing program efforts, two important projects were brought closer to fruition during FY 1975. First a contract was negotiated with JRB Associates, Inc. to provide an in-depth evaluation of the NIDR's periodontal disease research effort. It is the purpose of this evaluation to identify program strengths and weaknesses and provide reasonable guidelines by which program objectives can be accomplished.

The second effort, which actually began some two years ago, is an evaluation of the concept of the Dental Research Institutes/Centers as an instrument of science policy. With the assistance of Dr. John B. Macdonald, Executive Director, Council of Ontario Universities, NIDR staff has developed a preliminary outline to be utilized in data collection. A request for Proposals is being issued as the fiscal year ends.

In order to utilize the Institute's Council as a truly effective advisory body, it has been considered essential that it become more broadly and intimately acquainted with all NIDR programs. Accordingly, the practice of this Institute over recent years has been to present full and detailed annual reports of every research activity regardless of instrument of support, i.e., extramural, intramural and national caries programs. Beginning in November 1974, the Office of Collaborative Research also provided reports to the Council. This procedure will continue to be followed at future meetings so that Council may be fully appraised of the Institute's activities conducted under the contract mechanism.

Office of Scientific and Health Reports

The NIDR Office of Scientific and Health Reports (OSHR) is the primary point of contact between the Institute and the media, and a primary focus for identification and resolution of communication and public relations problems between the Institute and its various lay, scientific and professional publics.

The multiformity of the activities of the OSHR is determined by the six individual publics which NIDR must reach -- 1) the scientific research community; 2) the dental profession, including educators, practitioners, and researchers; 3) students, including dental students and high school students interested in science; 4) mass communication media such as the press, radio and television; 5) members of the Congress; and 6) the general public.

In the continuing effort to report the research findings of NIDR to the scientific community, quarterly distribution is made of Abstracts from NIDR Scientists, and copies of this publication are mailed to members of the dental section of the Pan American Health Organization.

During the year, this office served as the clearance center for manuscripts and abstracts prepared by NIDR investigators for publication or presentation. It also had the responsibility for securing the "concept clearance" now required by the DHEW before authorization can be obtained for the printing or reprinting of any publication. Other responsibilities included the preparation of the NIDR components of the NIH Annual Bibliography and Research Advances 1975.

In collaboration with Institute scientists, three exhibits were developed for display during the NIH Scientific staff alumni meeting and for exhibit during the entire bicentennial celebration.

The dental profession, including educators, practitioners and researchers, the National Advisory Dental Research Council, the subcommittee on appropriations of the House of Representatives, the American Dental Association, and local and state dental societies have all expressed interest in NIDR's efforts to keep dental practitioners more informed of dental research activities. In response, this office issues the monthly publication "Research News from NIDR", the quarterly publication "Research Capsules", and provides special news items to the Federation Dentaire Internationale.

A filmed report of the NIDR caries vaccine study--the first of a series of state-of-the-art films--has been prepared this year and is currently being circulated for use at state and county dental society meetings and in dental schools.

Continuing to serve as liaison between the scientists and the dental practitioner, this office prepared appropriate responses by letter or by telephone, to each requestor.

Three films, initiated by or produced with assistance from this office, received wide distribution during the year among students at the high school and dental school level. This office also supplied materials on careers in dental research; information for use in table clinics, science projects and health fairs; tours for visiting groups of students; and prepared a feature article for the Bulletin of the American Dental Student Association.

News releases, announcements, and press summaries reporting both intramural and extramural programs of the Institute were prepared. Radio spot announcements for release to 700 stations were prepared and taped radio interviews of dental scientists were arranged.

A television spot announcement, featuring a staff member of this office, was distributed. Requests from 11 states for the NIDR publication Research Explores Dental Decay have resulted from the widespread use of this brief announcement.

Special reports were prepared in response to requests from individual members of the Congress as well as from the Senate Appropriations Committee, and letters of reply were written for use by members of the Congress in answering constituent inquiries concerning dental research.

The general public's increasing concern with oral health problems is reflected in the inquiries received by this office. In addition to distributing the NIDR publications, individual responses were written and relevant supporting literature was supplied as required.

In cooperation with the staff of the National Caries Program, a pamphlet was developed to provide parents with information regarding the school mouth-rinse demonstration programs conducted by the NIDR. Also, an illustrated brochure presenting specific steps necessary in controlling bacterial plaque is currently being prepared for distribution.

The Scientific and Health Reports Officer served on the NIH Open House Committee that developed the first opportunity for the general public to visit the National Institutes of Health. Participation in this activity included the preparation of the program, the issuance of a brochure, and an exhibit manned by OSHR staff during the two-day NIH Open House, which was attended by approximately 30,000 persons.

In summary, as the NIDR's OSHR continues to serve as a centrepital force of innovation and interlocking activities of the Institute, its activities have included the preparation of research and program highlights; special reports to the Congress on NIDR programs; speeches for NIDR staff members and for use by the Secretary of DHEW; responses to 6,015 inquiries; development of three new exhibits; arrangements for nine showings of NIDR exhibits and manning exhibits at meetings attended by science teachers and the general public; distribution of approximately 71,100 pieces of literature; preparation of 88 press items (including summaries, releases, Research News from NIDR, NIH Record, Research Capsules, and FDI Newsletter); clearance of 178 manuscripts and abstracts; served as concept clearance center for institute publications; prepared 12 radio spot announcements and six Search for Health columns; accommodated 111 visitors to the NIDR and participated in NIH Open House activities; and prepared numerous internal reports, including weekly reports, manuscript reports, activity reports, NIDR Key Staff Listing, NIDR Publications List and NIDR's section of the NIH Almanac.

Planning, Analysis, and Evaluation Activities

This activity served as the focal point for planning, analysis, and evaluation within the Institute, provided responses on NIDR programs and activities to the NIH Associate Director for Program Planning and Evaluation, and represented the Institute at NIH meetings on planning and evaluation.

NIDR workshops and conferences supported by one percent set-aside funds were coordinated by this office and guidelines were provided to staff members on procedures and report requirements.

The major effort of this unit during FY 1975 was initiating, planning, and coordinating the evaluation of the NIDR extramural and intramural periodontal disease research programs. A contract was awarded to provide support for this evaluation. Inasmuch as this is the first comprehensive evaluation of an NIDR research program, it is possible that it may serve as the prototype for evaluating other program areas.

Reports emanating from this office have included NIDR's contribution to the NIH Forward Plan--FY 1977-1981, and interim and comprehensive reports on NIDR's use of one percent set-aside funds in FY 1975.

Other activities during the past year included participation in the 3-day STEP Module on Program Planning, Evaluation and Analysis; periodically meeting with a consultant developing a means of evaluating the five NIDR Dental Research Institutes/Centers; collaboration with NIDR's Dental Research Data Officer in providing guidance and data to the Science Information Exchange for two annual NIDR publications; and contribution to the preparation of texts on NIDR programs for budget presentations.

Financial Management Office

The Financial Management Office has the responsibility for the Institute's total budget program.

Serving as the Institute's center for budget data and related information, major activities of this office include the formulation of budget estimates, including the planning, development and review of funds required to support operating programs and future plans; the preparation and presentation of budget estimates; the determination of funds required within authorized limits; the administration of apportionments, allocations and allotments; and the management controls over obligations and the expenditure of funds.

The cyclic nature of budget administration is continuous but the activities and work operations of the Institute's financial requirements are constantly revised, modified and reorganized.

During the past year, the Financial Management Office continued to refine its use of the Wylbur and Autotab systems. These computer systems have increased the efficiency of the Office in the preparation of management reports on projected employment levels, travel reduction and space allocations. Also, by using these systems, analytical projections of obligation patterns for the cost centers were routinely prepared.

The issuance of monthly status reports on personnel and the rate of expenditures for program activities issued by this office provided the budget office and administrative program directors with a reliable guide to assist in maximizing their personnel and financial resources. In addition, these reports provide the management decision centers (Executive Office and Personnel Office) with timely financial information for their guidance.

The change from a 12-month budget cycle to a 15-month cycle necessitated extensive revision of budgetary data to compensate for the time extension. This change greatly increased the workload of the OFM during FY 1975. The NIDR Office of Financial Management continued to contribute to the overall programs of NIH by actively participating in the training programs for budget personnel. This Office has worked with four trainees during FY 1975 and the experience gained during their assignment with NIDR has been very beneficial in preparing these individuals for positions in budget offices.

The Financial Management Office continued to engage in such diverse activities as budget execution; payroll records, including corrections and additions; routine and special OFM reports, monthly status reports, reports on special management projects; grant forecasts, special reports concerning the utilization of impounded funds, and on-duty personnel reports.

Personnel Office

During the past year, the emphasis has been on communicating information and providing services.

The Personnel Office staff participated fully in the NIDR EEO Conference at Hunt Valley and in follow-up meetings, including the formation of the Affirmative Action Plan Task Force. A representative has also attended all meetings of the NIDR EEO Committee.

A series of meetings were held with secretarial and clerical personnel throughout the Institute in order to explain classification principles, training opportunities and career development strategies.

Of primary importance during FY 75, this office began a complete Personnel Review of the Institute. This review will encompass such areas of concern as position classification, position management, employee questions, career development, employee utilization, and personnel policies and regulations. During this review, all employees will be interviewed at the job site and a final report will be prepared for the Director.

Job restructuring activities have continued with emphasis on the situation of the dental assistants and the hygienist in the Office of the Clinical Director. In line with the increased research activities in the Dental Clinic, the dental assistants' positions have been restructured to include a variety of research duties which will upgrade their positions and also contribute substantially to research resources.

The Institute's manpower has been significantly increased through the usage of student hiring mechanisms. These mechanisms have provided additional assistance to senior investigators while giving training and economic assistance to high quality students.

Data Processing Systems and Analysis Section

The Data Processing Section is actively involved in the design, development and implementation of systems and procedures to provide useful, timely and accurate information to meet NIDR research and administrative needs. It is involved with intramural research projects as well as with the contracts and grants mechanism.

During the past year, the administrative unit of the Section developed a series of programs to provide status reports on research and training grants activity at each stage of the grants process. A booklet "Ask For It By Number" describing the system was prepared and distributed. A project to develop data on the Dental Research Manpower Pool was initiated.

The Contracts data system continued to provide regular reports on the status of collaborative research projects. Data from SSIE was interfaced with the NIDR system along with data on extramural projects.

Within the scientific applications unit a dual processor mini-computer system has continued to provide support to the NIDR research effort. This computer complex, primarily utilized for research effort in the intramural area, is connected to a variety of instruments--three scintillation counters, one amino acid analyzer, one X-ray diffractometer, one pH/turbidity control experiment, one neurophysiology stimulus response experiment, and one neurophysiology behavioral analysis experiment. During the past year, there have been significant increases in the demand for on-line services as requests to interface five other pieces of equipment have been received.

EEO Program

An EEO Coordinator was appointed in June 1974, to work in the Office of the Director as the primary source of information and guidance in matters pertinent to the Equal Employment Opportunity Programs of NIH and NIDR. In October 1974, a 2 1/2-day EEO Conference was attended by 83 NIDR employees who represented a cross section of the Institute by race, sex, laboratory classification, grade level and organization. The objectives of the conference were: 1) to develop awareness of the dimensions of racism and sexism; 2) to identify discriminatory barriers to career development for minorities and women; 3) to identify discriminatory barriers to career development due to institutional barriers; 4) to improve employee/supervisor relations through communications training; and 5) to develop action plans for systematic problem solving.

Nine groups, based on functional units within the NIDR, developed action plans which included training, communication of laboratory, promotion and training opportunities, promotion of individual recognition, improved communication, examination of the lack of advancement opportunities in secretarial positions, increasing the utilization of minorities and females in consultant groups, and elitism. The continuation of these initial action plans has varied in the individual organizational components.

In April 1975, this office participated in the Minority and Women's Opportunity and Resources Conference at NIH. Faculty and students from 75 minority and women's schools visited NIH. The NIDR held a workshop to familiarize interested participants with research programs at the NIDR, and to discuss research support available through grants and contracts, and employment opportunities.

The present activity of the NIDR's EEO program is concentrated on the development of an Affirmative Action Plan. A task force, representing a cross section of NIDR employees, is developing plans for the major areas of EEO concern: recruitment, placement and promotion training, development and upward mobility, supervisory and management development, employee relations, communications, and management of the EEO program.

Office of the Associate Director for Collaborative Research

In view of the increasing importance of the role played by contract supported research in accomplishing the goals and missions of the Institute, the Office of Collaborative Research was reorganized during FY 75 with the creation of the Office of the Associate Director for Collaborative Research. In order to increase efficiency in the operation of the office, two functional staffs have been created: the Contract Review Staff and the Contract Management Staff. The Contract Review Staff is responsible for the conduct of technical merit review of proposals received in response to requests for proposals as well as the review of interim progress and technical merit of selected on-going contracts. The Contract Management Staff is responsible for the issuance of RFP's, receipt of contract proposals, negotiation of contracts, and general business management of ongoing contracts. The Associate Director for Collaborative Research is responsible for the overall operation of the office, the development of policy and operational procedures, and is responsible for maintenance of liaison with other institutes of the NIH as well as with the scientific community in general.

Early in the fiscal year, the policies and procedures for the conduct of collaborative research activities were modofied and updated in order to bring them in line with the directives of the 1974 Cancer Act and recent NIH policy issuances. The major changes which have resulted from this action are: a) the establishment of a requirement for peer review of the concept of a contract prior to initiation of the contract; b) the establishment of a requirement for peer review of the progress and plans for certain ongoing contracts; c) a re-emphasis of the requirements for close post-award monitoring of active contracts; d) the updating of the requirements for review and monitoring of contracts involving human subjects for compliance with Departmental policy and ethical considerations; and e) the restructuring of the Contract Review Group in order to bring its activities into compliance with the Committee Management Act.

During FY 75 the Office of Collaborative Research has handled an unusually heavy workload. This is a consequence of increased funds for new contract activities which were made available by the completion of a number of contracts awarded from the omnibus RFP's issued in FY 71 and FY 72. During FY 75, the office issued 26 RFP's of which 23 were for competitive procurement and three were for Interagency Agreements. Of the 23 competitive RFP's, 144 proposals were received and, after initial technical merit review, 66 were found to be in the competitive range. When competitive range negotiations are completed, it is anticipated that 40 to 45 new contracts will be awarded prior to the end of the fiscal year. The large number of new contracts anticipated is accounted for by the planned award of several contracts to initiate caries prevention demonstration programs solicited by one RFP. In addition to the above, six bonafide unsolicited proposals were received during FY 75, all of which were rejected for either lack of program relevance or for lack of technical merit. In FY 75 we will have approximately 75 to 80 active contracts and 10 active Interagency Agreements. Support of the activities represents an expenditure of approximately $4.9 million.

During FY 75 the operation of the Office of Collaborative Research was reviewed by personnel of the Office of Administrative Management, Office of the Assistant Secretary of Health, DHEW. The review team was impressed by the fact that NIDR has established an outstanding record for competitive procurement, and the Institute is receiving recognition at the Departmental level for the manner in which it conducts its collaborative research activity.

Action is being taken to expedite the receipt of Requests to Initiate Contracts in the Office of Collaborative Research and to allow for issuance of RFP's earlier in the Fiscal Year, thus more evenly distributing the workload throughout the year.

Dental Research Data Officer

Partially fulfilling the Institute's responsibility to "promote the coordination of research conducted by the Institute, and similar researches conducted by other agencies, organizations, and individuals", the Dental Research Data Officer provides an active interface for the exchange of dental research information. Statistical and substantive data on dental and dentally-related research are collected, analyzed and disseminated routinely or on request.

The greatest number of requests for data are of the ad hoc variety which cover many different, and sometimes unusual, subject areas. These requests are difficult to respond to because the information is not readily available and must be defined and sorted out of the total data base.

A smaller number of requests are of the recurring type, and, once the need is known, the terms defined, and the key words assigned, the retrieval and compilation of a report is fairly routine. The number of these recurring requests is on the increase as new special interest groups receive more attention, but the response mechanism has been improved and is capable of accommodating this increase.

Statistically, there has been a 50% increase in the total number of requests over last year. Fifty-nine percent of the requests came from other components of the Federal Government; 32% originated within the Institute and 9% were non-Federal.

The source of information used in response to requests was about the same as last year; 71% from NIDR, 21% from other Federal agencies, and 8% from non-Federal sources. The increase in the use of NIDR sources over last year is attributed to our growing dependence on and the increased effect of the Data Processing Systems and Analysis Section.

In recognition of the kinds of statistical, scientific and technical information most often sought, a number of publications have been developed to compile, transmit and more permanently record these data. Current titles include, National Institute of Dental Research Annual Report, Trainees and Fellows Supported by the National Institute of Dental Research, National Institute of Dental Research Programs, and Dental Research in the United States, Canada, and Great Britain. It should be mentioned that the Programs title supercedes

the National Institute of Dental Research Grants and Awards publication of previous years because the contents have been expanded to include research contracts, interagency agreements, and intramural projects in addition to grants and awards. Comments and frequent inquiries about our publications affirm that they serve a useful purpose in the overall process of scientific communication.

Our bases of information are constantly being updated and expanded. The manual system has been greatly improved during the last year and nicely augments the computer with certain advantages in time and comprehensiveness. A formalized search strategy has begun to materialize for the more frequent requests--those that involve NIDR-support in various areas-- and we plan to give this additional attention in the next year.

This year a bibliographic service for technical reports has been initiated. The reports that emanate from federally-sponsored contracts, including our own, are filled with the National Technical Information Service. On a regular basis we receive copies of these reports related to dentistry, the biological sciences, prosthetics and mechanical organs, adhesives and sealants, information systems, and reference materials.

The reports, in microfiche form, are reviewed, classified, and announced by means of a selective bibliography to all interested investigators within the Institute. The basic purpose, of course, is to have our NIDR-sponsored contractors' technical reports organized, on file and available. NIDR scientists or program leaders may request a copy of the report for their own use. The response has been most heartening and we plan to continue it for another year.

In an attempt to better understand how dental scientists communicate so as to enhance the research process, we developed a request for a proposal to study the "Exchange of Scientific Information in Dental Research". Bidder response was most enthusiastic and the initial review group had to select from a record number (23) of proposals. Unfortunately, negotiations were abandoned because the bids exceeded the DHEW-approved Health Evaluation Plan estimates and because of changes of priority in program need.

With completion of the Extramural Program's Manpower Management System, there has been considerable interest on the part of NIH components to hear more about that and, to date, presentations involving the Dental Research Data Officer have been made to the National Institute of Child Health and Human Development, Executive Committee for Extramural Affairs, Grants Associates, and NIH Health Scientist Administrators. Similar presentations are anticipated for the future. At the request of the Chief Dental Officer, the Research Data Officer served as the Public Health Service observer and reporter to the Reference Committee on Scientific Matters at the Annual Meeting of the American Dental Association.

NIDR ANNUAL REPORT

RESEARCH PROJECTS AND INDEXES

Introduction

This section of the NIDR Annual Report, on blue paper, is devoted to intramural individual project reports. The SSIE Notice of Research Project form (PHS 166) has been modified to include the data requested by NIH for individual projects. This eliminates some duplication of effort and makes for a more useful project description format. More lengthy discussions of the intramural research effort are to be found in Part II and Part IV. All of the bibliographic information appears in the Scientific Directory and Annual Bibliography published by NIH.

A major change in the individual project report this year has been made in the format of the project number. The "Z01" prefix has been added to differentiate intramural projects from other types of support in the DRG data base. The "DE" identifies the project as belonging to NIDR. This is followed by a five-digit number that will be assigned to the project throughout its life-time. The final two digits indicate the number of years that the project has been in existence. The first set of letters following the number is the accepted abbreviation for the laboratory or branch responsible for the project and the final letter is the investigators' concept of whether the research is applied (A), basic (B), or clinical (C).

The NIDR Scientific Classification number is assigned by the investigator from a Code List provided for that purpose and is used primarily for budget and planning purposes. The investigator is also requested to underline keywords or concepts in the title and description of each project. The Dental Research Data Officer reviews this material and prepares a list of keywords that are used to retrieve projects by subjects for the various requests directed to his office. For the most part, these keywords are made to conform to those used by the National Library of Medicine in its Medical Subject Headings (MeSH). When suitable terms are not found in MeSH, reference is made to the NIH Medical and Health Related Sciences Thesaurus, Dorland's Medical Dictionary, or the investigator's own words in that order, and an (*) appears to indicate that it is a non-MeSH term. Users are advised to consult these publications if unable to find projects in the Subject Index.

The Indexes for the Annual Report are prepared with the assistance of the Data Processing Systems and Analysis Section.

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HYALURONIC ACID	D	111
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HYDROXYAPATITE	D	109
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IMMUNIZATION	E	112
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IMMUNOGENETICS	G	60
IMMUNOLOGIC DISEASES	C	98
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INFANT, NEWBORN	M	88
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INFLAMMATION	C	21
INFLAMMATION	C	4
INFLAMMATION	C	6
INFLAMMATION	C	32
INFLAMMATION	C	40
INFLAMMATION	C	42
INFORMATION RETRIEVAL SYSTEMS	L	30

* NON-MESH TERM

SUBJECT AREA	CATEGORY	PAGE
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INTERFERON	D	98
ISOENZYMES	D	121
KERATOSIS	C	7
LABORATORIES	N	18
LAVAGE *	E	85
LEUKOCYTES	A	4
LIPASE	D	122
LUNG	A	6
LYMPHOCYTE TRANSFORMATION	G	89
LYMPHOCYTES	A	41
LYMPHOCYTES	A	22
LYMPHOCYTES	A	99
LYMPHOCYTES	A	59
LYMPHOCYTES	A	60
LYMPHOCYTES	A	61
LYMPHOCYTES	A	93
LYMPHOCYTES	A	32
LYMPHOCYTES	A	101
LYMPHOCYTES	A	31
LYMPHOCYTES	A	98
LYMPHOCYTES	A	117
LYMPHOKINES	D	98
LYMPHOKINES	D	22
MACROPHAGES	A	31
MACROPHAGES	A	117
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MALFORMATIONS *	C	14
MEDICAL ILLUSTRATION	G	34
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METABOLISM	G	116
METABOLISM	G	28
METABOLISM	G	5
METABOLISM, INBORN ERRORS	C	57
METHOHEXITAL	D	94
MICE	B	14
MICE	B	59
MICE	B	57
MICE	B	60
MICE	B	74
MICE	B	80
MICE	B	24
MICE	B	41
MICROORGANISMS *	B	115

* NON-MESH TERM

SUBJECT AREA	CATEGORY	PAGE
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MONKEYS	B	12
MONKEYS	B	27
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MONKEYS	B	58
MONKEYS	B	90
MONKEYS	B	113
MONKEYS	B	55
MOTTLED ENAMEL	C	17
MOUTH MUCOSA	A	7
MOUTHWASHES	D	50
MUCOPOLYSACCHARIDES	D	96
MUCOPOLYSACCHARIDES	D	119
MUTAGENS	D	118
MYXOMYCETES	B	4
NEUROPHYSIOLOGY	G	39
NEUROPHYSIOLOGY	G	19
NUCLEAR MAGNETIC RESONANCE	H	119
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ORAL MANISFESTATIONS	C	67
OSTEITIS	C	85
PAIN	C	95
PAIN	C	114
PAIN	C	33
PALATE	A	111
PANCREATIC NEOPLASMS	C	121
PANCREATITIS	C	121
PAROTID GLAND	A	53
PERCEPTION	F	56
PERIODONTAL DISEASES	C	89
PERIODONTAL DISEASES	C	74
PHOSPHOROFLUORIDATE *	D	48
PHOSPHOTRANSFERASES	D	38

* NON-MESH TERM

SUBJECT AREA	CATEGORY	PAGE
PHYSICAL STIMULATION	E	27
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PHYSICAL STIMULATION	E	113
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POLYSACCHARIDES	D	47
POLYSACCHARIDES	D	116
POLYSACCHARIDES	D	36
POLYSACCHARIDES	D	29
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RATS	B	83
RATS	B	82
RATS	B	104
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RATS	B	71
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RATS	B	12
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RATS	B	105
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RNA	D	92
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SALIVA	A	109
SALIVARY GLANDS	A	122
SALIVARY GLANDS	A	110
SALIVARY GLANDS	A	16
SEMEN	A	35
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SENSATION	F	56
SEPTICEMIA	C	65
SEPTICEMIA	C	84

* NON-MESH TERM

SUBJECT AREA	CATEGORY	PAGE
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SJOGREN'S SYNDROME	C	53
SJOGREN'S SYNDROME	C	115
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STATISTICS	H	70
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STOMATITIS, APHTHOUS	C	66
STOMATITIS, APHTHOUS	C	67
STOMATITIS, APHTHOUS	C	91
STREPTOCOCCUS	B	83
STREPTOCOCCUS	B	82
STREPTOCOCCUS	B	75
STREPTOCOCCUS	B	68
STREPTOCOCCUS	B	118
STREPTOCOCCUS	B	71
STREPTOCOCCUS	B	58
STREPTOCOCCUS	B	5
STREPTOCOCCUS	B	54
STREPTOCOCCUS	B	43
STREPTOCOCCUS	B	44
STREPTOCOCCUS	B	47
STREPTOCOCCUS	B	36
STREPTOCOCCUS	B	28
STREPTOCOCCUS	B	29
STREPTOCOCCUS	B	38
SUBLIMAZE *	D	94
SUGAR ALCOHOLS	D	38
SURGERY	E	85
SURGERY	E	84
SURGERY, ORAL	E	94
TABLETS	D	49
TAIL	A	103
TASTE	F	88
TASTE	F	56
TEICHOIC ACID *	D	116
TERATOGENIC AGENTS *	D	100
TETRACYCLINE	D	51
TETRACYCLINE	D	9
TETRACYCLINE	D	62

* NON-MESH TERM

SUBJECT AREA	CATEGORY	PAGE
TONGUE	A	88
TOOTH	A	83
TOOTH	A	8
TRANSGLUTAMINASES *	D	1
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TRIGEMINAL NERVE	A	113
TRIGEMINAL NERVE	A	27
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UREMIA	C	51
VACCINES	D	58
VAGINAL DISEASES	C	87
VIRUS DISEASES	C	87
VIRUS DISEASES	C	76
VIRUSES	B	77
VIRUSES	B	57
VIRUSES	B	91
VIRUSES	B	61
VIRUSES	B	67
VIRUSES	B	112
VIRUSES	B	98
VITAMIN A	D	97
VITAMIN B12	D	82
WATER	D	17
WHEAT	B	92
WOMEN	M	87
WOUND HEALING	G	35
X-RAY DIFFRACTION	H	51
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* NON-MESH TERM

NIDR ANNUAL REPORT - FY 75

INDEX

RESEARCH PROJECTS BY TYPE OF RESEARCH

APPLIED	BASIC		CLINICAL
DE00005-18	DE00001-24	DE00083-02	DE00029-08
DE00011-13	DE00002-24	DE00084-02	DE00037-06
DE00019-10	DE00006-15	DE00087-02	DE00045-05
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DE00031-07	DE00009-14	DE00094-02	DE00066-04
DE00032-07	DE00012-13	DE00108-02	DE00070-03
DE00039-06	DE00015-13	DE00110-02	DE00071-03
DE00044-05	DE00018-11	DE00111-02	DE00075-03
DE00047-04	DE00020-10	DE00114-02	DE00085-02
DE00056-04	DE00022-10	DE00123-02	DE00086-02
DE00064-04	DE00024-09	DE00124-02	DE00089-02
DE00077-02	DE00025-09	DE00131-01	DE00091-02
DE00079-02	DE00028-08	DE00134-01	DE00096-02
DE00081-02	DE00034-07	DE00135-01	DE00109-02
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DE00098-02	DE00038-06	DE00137-01	DE00113-02
DE00101-02	DE00040-06	DE00139-01	DE00118-02
DE00102-02	DE00042-05	DE00141-01	DE00119-02
DE00103-02	DE00043-05	DE00142-01	DE00127-02
DE00115-02	DE00046-05	DE00143-01	DE00128-02
DE00116-02	DE00048-04	DE00144-01	DE00129-01
DE00117-02	DE00049-04	DE00145-01	DE00132-01
DE00122-02	DE00050-04	DE00147-01	DE00159-01
DE00130-01	DE00055-04	DE00148-01	
DE00133-01	DE00058-04	DE00149-01	
DE00138-01	DE00060-04	DE00150-01	
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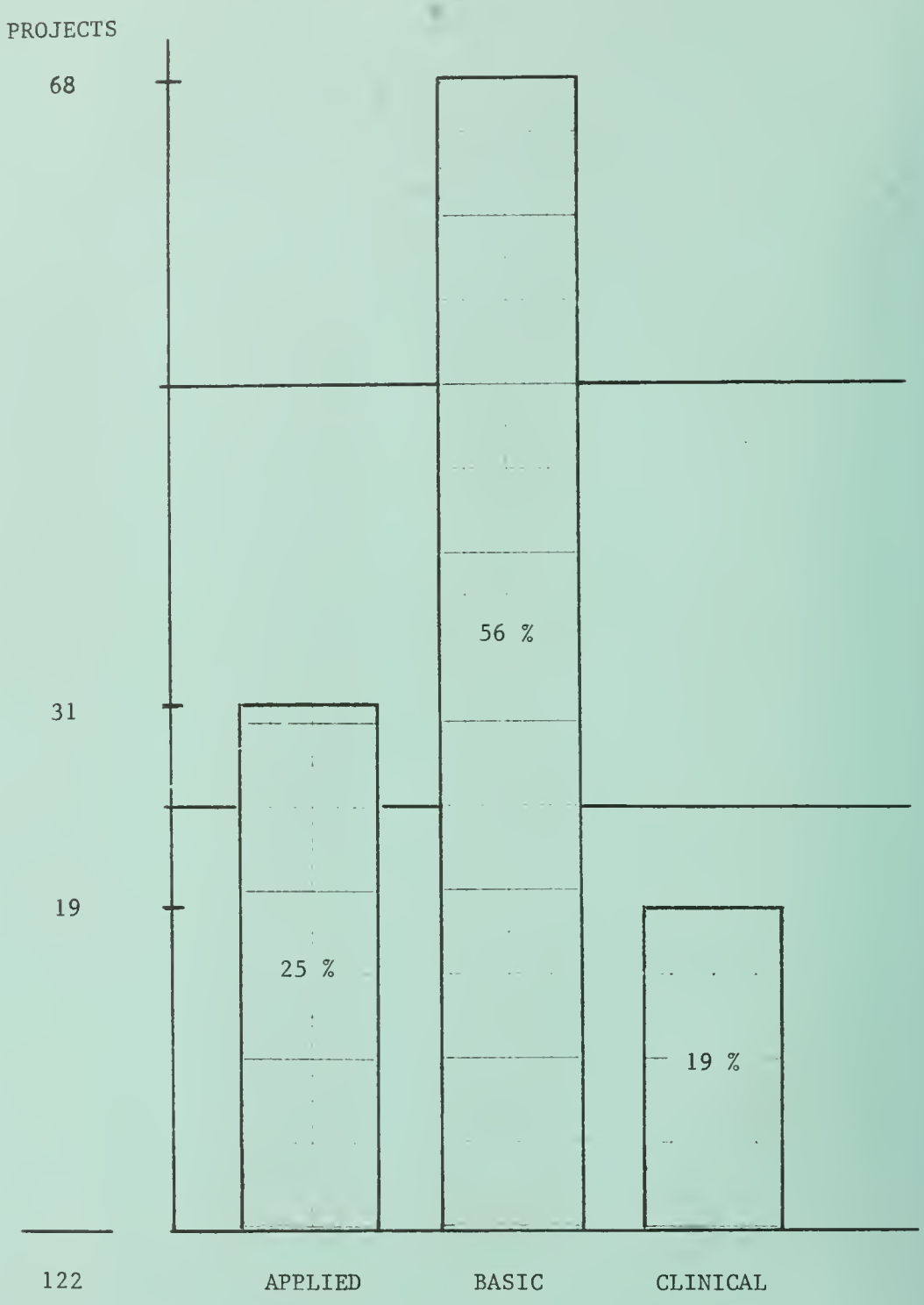
DE00146-01	DE00063-04	DE00152-01	
DE00156-01	DE00067-03	DE00153-01	
DE00158-01	DE00068-03	DE00154-01	
DE00161-01	DE00073-03	DE00155-01	
	DE00074-03	DE00157-01	
	DE00078-02	DE00160-01	
	DE00080-02		
TOTAL 31	TOTAL 68		TOTAL 19
(25%)	(56%)		(19%)

BY TYPE OF RESEARCH AS DESIGNATED BY THE PRINCIPAL INVESTIGATOR

RESEARCH PROJECTS BY TYPE OF RESEARCH FY 1975



BY TYPE OF RESEARCH AS DESIGNATED BY THE PRINCIPAL INVESTIGATOR

NATIONAL INSTITUTE OF DENTAL RESEARCH

Classification Guide

CATEGORIES and SUBJECTS

A Anatomical Terms

B Organisms

C Diseases

D Chemicals and Drugs

E Analytical, Diagnostic and Therapeutic Technics and Equipment

F Psychiatry and Psychology

G Biological Sciences

H Physical Sciences

I Anthropology, Education, Sociology and Social Phenomena

J Technology, Commerce and Industry

K Humanities

L Communication, Library Science, and Documentation

M Named Groups of Persons

N Health Care

CATEGORY A

ANATOMICAL TERMS

BASOPHILS
BLOOD VESSELS
BLOOD
BONE AND BONES
CONNECTIVE TISSUE
DENTAL ENAMEL
DENTITION
EPITHELIAL CELLS
FACE
FECES
FETUS
GANGLIA
GANGLIA, AUTONOMIC
HEAD
LEUKOCYTES
LUNG
LYMPHOCYTES
MACROPHAGES
MOUTH MUCOSA
PALATE
PAROTID GLAND
RECEPTORS, NEURAL
SALIVA
SALIVARY GLANDS
SEMEN
SKIN
TAIL
TONGUE
TOOTH
TRIGEMINAL NERVE

CATEGORY B

ORGANISMS

ACTINOMYCES
ASCARIS
BACTERIA
CATS
CHICKENS
CORN
MICE
MICROORGANISMS *
MONKEYS
MYXOMYCETES
RATS
STREPTOCOCCUS
VIRUSES
WHEAT

CATEGORY C

DISEASES

AUTOIMMUNE DISEASES
BEHCET'S SYNDROME
CLEFT PALATE
DEATH, SUDDEN
DENTAL CARIES
DENTAL ENAMEL HYPOPLASIA
DENTAL PLAQUE
DENTAL CARIES
DIABETES *
DIABETES INSIPIDUS
DIABETES MELLITUS
ENDOCRINE DISEASES
GINGIVITIS
HERPES SIMPLEX
HERPESVIRUS INFECTIONS
HYPERPLASIA
HYPOPHOSPHATEMIA, FAMILIAL
IMMUNOLOGIC DISEASES
INFECTION
INFLAMMATION
KERATOSIS
MALFORMATIONS *
METABOLIC DISEASES
METABOLISM, INBORN ERRORS
MOTTLED ENAMEL
ORAL MANISFESTATIONS
OSTEITIS
PAIN
PANCREATIC NEOPLASMS
PANCREATITIS
PERIODONTAL DISEASES
PRECANCEROUS CONDITIONS
PSEUDOHYPOPARATHYROIDISM
SEPTICEMIA
SJOGREN'S SYNDROME
STOMATITIS, APHTHOUS
UREMIA
VAGINAL DISEASES
VIRUS DISEASES
XEROSTOMIA

CATEGORY D

CHEMICALS AND DRUGS

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ADHESIVE SEALANTS *
AMYLASE
ANTI-INFECTIVE AGENTS
ANTIBIOTICS
ANTIBODIES
ANTICARIES AGENTS *
ANTIGENS
ANTIPLAQUE AGENTS *
APATITES
CALCIUM PHOSPHATES
CALCIUM RADIOSOTOPES
CARBOHYDRATES
COLLAGEN
COMPLEMENT
CYANCOBALAMIN *
DIAZEPAM
ELASTIN
ENDOTOXINS
ENZYMES
FLUORIDES
GLUCANS *
GLUCOSYLTRANSFERASES
GLYCOPROTEINS
HYALURONIC ACID
HYDROXYAPATITE
HYPNOTICS AND SEDATIVES
IGE
IMMUNOSUPPRESSIVE AGENTS
INSULIN
INTERFERON
ISOENZYMES
LIPASE
LYMPHOKINES
METHOHEXITAL
MINERALS
MITOGENS
MOUTHWASHES
MUCOPOLYSACCHARIDES
MUTAGENS
PHOSPHOROFLUORIDATE *
PHOSPHOTRANSFERASES
PLANT AGGLUTININS
PILOCARPINE
POLYSACCHARIDES
PROTEINS
RNA
STEROIDS
SUBLIMAZE *
SUGAR ALCOHOLS
TABLETS
TEICHOIC ACID *
TERATOGENIC AGENTS *
TETRACYCLINE
TRANSGLUTAMINASES *
VACCINES
VITAMIN A
VITAMIN B12
WATER
8-HYDROXYQUINOLINES *

CATEGORY E

ANALYTICAL, DIAGNOSTIC AND THERAPEUTIC TECHNIC S AND EQUIPMENT

ANALGESIA
BACTERIOLOGICAL TECHNICS
BLOCKING *
CEPHALOMETRY
CLINICAL TRIALS *
DIAGNOSIS
DIAGNOSIS, ORAL
DIET
DMF INDEX
HISTOCYTOCHEMISTRY
IMMUNIZATION
IMMUNOFLUORESCENCE TECHNIC
IMMUNOLOGIC TECHNICS
IMPLANTS *
LAVAGE *
MICROSCOPY
MICROSCOPY, ELECTRON
PHYSICAL STIMULATION
POPULATION RESEARCH *
RADIOGRAPHY
RADIOGRAPHY, DENTAL
RADIOIMMUNOASSAY
SPECTROPHOTOMETRY
SURGERY
SURGERY, ORAL

CATEGORY F

PSYCHIATRY AND PSYCHOLOGY

BEHAVIORAL SCIENCES
DISCRIMINATION
FAMILY
PERCEPTION
SENSATION
TASTE

CATEGORY G

BIOLOGICAL SCIENCES

ANATOMY
ANTIBODY FORMATION
BIOCHEMISTRY
BIOLOGICAL TRANSPORT
BLOOD COAGULATION
CHEMOTAXIS
CLEFT LIP
EMBRYOLOGY
EVOLUTION
FERTILIZATION
FLUORIDATION
GENETICS
GERM-FREE LIFE
GROWTH
HISTAMINE LIBERATION
IMMUNITY, CELLULAR
IMMUNOGENETICS
IMMUNOLOGY
LYMPHOCYTE TRANSFORMATION
MEDICAL ILLUSTRATION
METABOLISM
MINERALIZATION *
NEUROPHYSIOLOGY
TRANSMISSION *
TWINS
WOUND HEALING

CATEGORY H

PHYSICAL SCIENCES

CHEMISTRY, PHYSICAL
HEAT
MODELS, BIOLOGICAL
NUCLEAR MAGNETIC RESONANCE
SPECTRUM ANALYSIS
STATISTICS
X-RAY DIFFRACTION

CATEGORY J

TECHNOLOGY, COMMERCE AND INDUSTRY

AUTOMATION
NUTS

CATEGORY L

COMMUNICATION, LIBRARY SCIENCE, AND DOCUMENT TION

COMPUTERS
INFORMATION RETRIEVAL SYSTEMS

CATEGORY M

NAMED GROUPS OF PERSONS

CHILD
INFANT, NEWBORN
WOMEN

CATEGORY N

HEALTH CARE

LABORATORIES

NON-MESH TERMS

SUBJECTS	CATEGORY
ACTINOBOLIN *	D
ADHESIVE SEALANTS *	D
ANTICARIES AGENTS *	D
ANTIPLAQUE AGENTS *	D
BLOCKING *	E
CLINICAL TRIALS *	E
CYANCOBALAMIN *	D
DIABETES *	C
GLUCANS *	D
IMPLANTS *	E
LAVAGE *	E
MALFORMATIONS *	C
MICROORGANISMS *	B
MINERALIZATION *	G
PHOSPHOROFLUORIDATE *	D
POPULATION RESEARCH *	E
SUBLIMAZE *	D
TEICHOIC ACID *	D
TERATOGENIC AGENTS *	D
TRANSGLUTAMINASES *	D
TRANSMISSION *	G
8-HYDROXYQUINOLINES *	D

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-52B-001

NIDR- Z01 DE 00001-24 LBC B

TITLE OF PROJECT

Chemical, Stereochemical and Conformational Aspects of Transglutaminases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI :	J. E. Folk	Chief, Enzyme Chemistry Section,	LB, NIDR
OTHERS:	R. J. Knights	Postdoctorate Fellow	LB, NIDR
	J. Schrode	Postdoctorate Fellow	LB, NIDR

COOP : None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section : Enzyme Chemistry
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Active site mapping studies on transglutaminases using model substrates will continue Special emphasis is being placed on the blood coagulation transglutaminases (plasma and platelet factor XIII) using a series of glutamine-containing peptide derivatives of amino acid sequences known to occur in the cross-linking regions of mammalian fibrins. Selective limited cleavages of the transglutaminases are being carried out using chemical agents and proteolytic enzymes. Subunit structures, subunit dissociations, and reassociations are under investigation. The purpose of these studies is to relate the structure of the transglutaminases to their catalytic function and to determine the common structural features of these enzymes which have very similar catalytic functions and mechanisms.

SPECIAL DESCRIPTORS:	Blood
NIDR CLASSIFICATION:	20325
TOTAL MAN YEARS :	4.00
PROFESSIONAL :	2.00
OTHER :	2.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	J. E. Folk	5/2/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

Prepared for the Science Information Exchange.

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-52B-002

NIDR Z01 DE 00002-24 LCB B

TITLE OF PROJECT

Chemical and Structural Studies on Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI :	K. A. Piez	Chief	LB NIDR
OTHERS:	L. L. Faltz	Research Associate	LB NIDR
	D. Martin	NIH Postdoctorate Fellow	LB NIDR
	B. R. Williams	Staff Fellow	LB NIDR
	G. Chandrakasan	Visiting Fellow	LB NIDR

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section : Protein Chemistry
Location : NIDR, NIH, Bethesda, MD 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is the long range purpose of this project to study the chemistry and structure of collagen from the molecular to the fiber level. The topics of present interest are:

1. The chemistry and molecular form of Ascaris cuticle collagen.
2. The improvement of methods to isolate intact native collagen monomer.
3. The characterization of collagen fibril structure by the introduction and location of artificial crosslinks.
4. The relationship of the amino acid sequence of collagen to the fibril structure.
5. The mechanism of collagen fibril formation.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20230
TOTAL MAN YEARS :	9.00
PROFESSIONAL :	4.50
OTHER :	4.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	[signature]	May 2, 1975

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-58A-005

Z01 DE 00005-18 LDBA A

TITLE OF PROJECT

Characteristics of Families with Oral Clefts and Oral Diseases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Niswander, Jerry D.	Dental Director	LDBA	NIDR
COPI:	Johnston, Malcolm C.	Visiting Scientist	LDBA	NIDR
OTHER:	Bingle, Glenn J.	Surgeon	LDBA	NIDR
	Chung, C. S.			(1)
COOP:	(1) School of Public Health, University of Hawaii Lancaster Cleft Palate Clinic, Lancaster, PA			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalies
Section: Genetics and Epidemiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project is designed to determine 1) if there are physical stigmata particularly changes in facial morphology associated with oral clefts, which are familial in nature and may be useful in clarifying the role of genetic (and environmental) factors in the etiology and pathogenesis in these anomalies. Of particular interest is the study of various characteristics obtained from cephalometric radiographs of affected individuals as well as their "normal" relatives including twins. Other objectives are 2) to develop methods to identify and classify heterogeneous subtypes of oral clefts and to identify individuals who are genetically at high risk, 3) to determine if maternal factors play a significant role in the etiology of oral clefts and 4) to study the incidence, type and significance of cardiovascular anomalies in patients with clefts, 5) to determine whether an association between reproductive intervals and oral facial clefts exists. 6) to determine the effects of inbreeding and hybridization on malocclusion and dental caries, 7) to assess the role of environment in the etiology of malocclusion and to assess the correlation between relatives with malocclusion and 8) to elucidate genetic factors related to morphological variation in teeth.

SPECIAL DESCRIPTORS:	Human, Population Research
NIDR CLASSIFICATION:	42240
TOTAL MAN YEARS:	2.25
PROFESSIONAL:	2.00
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	CO Malcolm C Johnston	4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-61B-006

Z01 DE 00006-15 LDBA B

TITLE OF PROJECT

Studies on Chemotaxis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Schiffmann, Elliott	Research Chemist	LDBA	NIDR
OTHER:	Aswanikumar, S.	Visiting Fellow	LDBA	NIDR
	Corcoran, Barbara A.	Chemist	LDBA	NIDR
	Notkins, Abner	Chief of LOM	LOM	NIDR
	Sandberg, Ann	Research Biologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomali
Section: Connective Tissue
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

We are attempting to gain insight into the biochemical processes of cell migration along a chemical gradient. While cells such as leucocytes, bacteria, and the cellular slime molds all show chemotactic behavior, we have focused upon the leucocyte. Efforts have proceeded in two directions: the characterization of leucoattractants released by bacteria and studies on the initial interaction between the attractant and the cell. Bacterial factors are heterogeneous, low molecular weight peptides, and it has been found that small formylmethionyl peptides, possibly related to the bacterial factors, are potent attractants for leucocytes. It is proposed to characterize further the bacterial factors and to investigate the mode of action of the well characterized fMet peptides on cellular migration. Obtaining such information may help to define further inflammatory events in general.

SPECIAL DESCRIPTORS:	Blood
NIDR CLASSIFICATION:	20312
TOTAL MAN YEARS:	2.75
PROFESSIONAL:	2.50
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Elliott Schiffmann	4/22/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-61B-007

Z01 DE 00007-15 LMI B

TITLE OF PROJECT

Studies on the Regulation of Carbohydrate Metabolism and Lactic Acid Production in Oral Microorganisms

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wittenberger, Charles L.	Chief, Microbiology Section	LMI	NIDR
COPI:	None			
OTHER:	Palumbo, M. P.	Chemist	LMI	NIDR
	Lee, Linda	Chemist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Microbiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The mechanisms by which cariogenic and noncariogenic Streptococci and certain members of the genus Actinomyces regulate the distribution of substrate carbon among multiple catabolic pathways is under investigation. Several enzymes, which function in the constitutive pathways that lead to lactic acid, have been identified as specific control sites. The means by which the catalytic function of these enzymes is modulated by their interaction with specific low molecular weight ligands is being studied. These comparative studies with cariogenic and noncariogenic streptococci are designed to gain insight into a possible biochemical basis for pathogenicity and ultimately to formulate a rational approach for its control.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	10140, 20212
TOTAL MAN YEARS:	1.50
PROFESSIONAL:	0.50
OTHER:	1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	C. L. Wittenberger	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00009-14 LDBA B

Prev. Ser. No. NIDR-62B-009

TITLE OF PROJECT

The Chemistry and Biosynthesis of Connective Tissue

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Martin, George R.	Chief of LDBA	LDBA	NIDR
OTHER:	Burks, James	Guest Worker	LDBA	NIDR
	McGoodwin, Ermona	Biologist	LDBA	NIDR
	Orkin, Roslyn	Fellow	LDBA	NIDR
	Smith, Barbara	Research Chemist	LDBA	NIDR
	Wahl, Larry	Staff Fellow	LDBA	NIDR
COOP:	Department of Medicine, Johns Hopkins Hospital, Baltimore, Maryland			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalie
Section: Connective Tissue Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this project is to study the formation and destruction of connective tissue in normal and disease states. Particular attention is directed toward collagen and proleoglycan. Current active aspects of this project include the isolation and characterization of precursor forms of collagen, the nature of the matrix in various tumors, the structure of basement membrane and the regulation of collagenase production by macrophages.

SPECIAL DESCRIPTORS: Blood vessels, Lung
NIDR CLASSIFICATION: 20322
TOTAL MAN YEARS: 12.25
PROFESSIONAL: 8.00
OTHER: 4.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	George R. Martin	4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev.Ser.No. NIDR-63A-011

Z01 DE 00011-13 LOM A

TITLE OF PROJECT

Clinico-pathologic Studies of Human Oral Mucosa

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Archard, Howell O.	Dental Director	LOM	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR/NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Human oral mucosal lesions of a keratotic nature are studies clinically and histologically over their duration for changes occurring in them. Lesions studied include hyperplastic, pre-malignant, and inherited mucosal disorders. Each case undergoes a detailed environmental analysis, appropriate laboratory studies are performed, and a record of the clinical and histologic changes is obtained in order to document the clinicopathologic progression of the disease.

Where indicated, appropriate correlative studies, such as histochemistry, electron microscopy, biodynamic (turnover) studies, immunofluorescent procedures, etc., are employed to provide additional significant data.

ECIAL DESCRIPTORS:	Human
DR CLASSIFICATION:	32300
TAL MAN YEARS:	.20
OFESSIONAL	.20
HER	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. O. Archard	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00012-13 LBS B

Prev. Ser. No. NIDR-63B-012

TITLE OF PROJECT

Infrared and Raman Spectroscopic Studies of Teeth and Bones and Related Synthetic Compounds

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Fowler, Bruce O.	Chemist	LBS	NIDR
COPI:	None			
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The main objective is to determine compositional and structural details of the inorganic phase in teeth and bones. Infrared (4000-60 cm^{-1}) and Raman spectroscopy as well as chemical methods are employed in these studies. Methods are devised for preparation of synthetic calcium apatites of controlled physical properties (crystal size and perfection) and chemical composition containing biologically relevant constituents, e.g., hydroxyl, fluoride, chloride, carbonate, water and acid phosphate. The vibrational spectra of these apatites and related compounds are assigned and characterized. Isotopically enriched apatite analogs are prepared to facilitate spectral assignments. The spectroscopic assignments and supplemental spectral data (temperature dependency and polarization) are utilized to establish compositional and structural details of the apatites which include the type and geometry of ions, the site or number of sites occupied by ions, orientation of ions, chemical bonding and interactions of ions and semi-quantitative estimations of constituents present. The results of findings for the controlled apatite system are related to the inorganic phase in calcified tissues.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10210
TOTAL MAN YEARS:	1.00
PROFESSIONAL:	1.00
OTHER:	None

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Bruce O. Fowler	22 April 1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-63B-015

Z01 DE 00015-13 LBS B

TITLE OF PROJECT

Experimentally Induced Enamel Defects

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Nylen, Marie U. Chief, Lab. of Bio. Structure LBS NIDR
COPI: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Previous studies have demonstrated that intraperitoneal injections of tetracycline hydrochloride to Sprague-Dawley rats can give rise to hypoplastic lesions in the enamel of any tooth that is under formation at the time of drug administration. The aim of the investigation this past year has been to define in detail the relationship of dose size, number of injections, concentration of drug and age of the experimental animal to serum levels of the antibiotic and incidence of enamel and dentin defects. In addition to these studies experiments have been initiated aimed at establishing the effect of tetracycline on the conversion of amorphous calcium phosphate to crystalline hydroxy apatite in both an in vitro and in vivo system.

SPECIAL DESCRIPTORS: Children
NIDR CLASSIFICATION: 10300
TOTAL MAN YEARS: 3.
PROFESSIONAL: 1
OTHER: 2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
ational Institute of Dental Research	Marie U. Nylen	4/23-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-65B-018

Z01 DE 00018-11 NAB B

TITLE OF PROJECT

The Response of Neurons in the Trigeminal Ganglion to Innocuous and Noxious Stimuli

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dubner, Ronald	Dent Dir, Ch Neurobiol Anesth Br	NAB	NIDR
COPI:	Beitel, Ralph E.	Senior Staff Fellow	NAB	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Microelectrode recordings from the trigeminal ganglion are performed in anesthetized monkeys. Mechanical, thermal, and noxious stimuli are applied to the face and oral mucosa and the response properties of single neurons are recorded and stored on magnetic tape. Data is analyzed with the aid of an on-line, real-time computer system.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	60210
TOTAL MAN YEARS:	1.25
PROFESSIONAL	.75
OTHER	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	[signature]	[illegible]

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser.No. NIDR-66A-019

Z01 DE 00019-10 LOM A

TITLE OF PROJECT

Clinical and Morphologic Studies of the Human Dentition in Acquired and Inherited Metabolic Diseases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Archard, Howell O.	Dental Director	LOM	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR/NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Clinical and morphologic characteristics of the deciduous and permanent teeth of individuals affected with a wide variety of inherited or acquired metabolic diseases are studied. The gross and microscopic changes in the teeth are recorded, and correlations with the developmental events and general metabolic changes are undertaken.

Teeth removed from patients with metabolic disease who have been studied at the Clinical Center of the National Institutes of Health, comprise the major source of material, although specimens from outside sources are studied as well. Disorders currently under study include: Hereditary hypophosphatemia (Vitamin D-resistant rickets), hypophosphatasia, pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism, Hurler's syndrome, diabetes insipidus, ectodermal dysplasia, chronic Vitamin D intoxication, infantile hypercalcemia, primary hyperoxaluria, etc.

SPECIAL DESCRIPTORS:	Human and Children
NIDR CLASSIFICATION:	10210
TOTAL MAN YEARS:	.05
PROFESSIONAL:	.05
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. O. Archard	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00020-10 NAB B

Prev. Ser. No. NIDR-66B-020

TITLE OF PROJECT

Anatomical studies of the organization of the main sensory and spinal trigeminal nuclei

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Gobel, Stephen	Sr Dental Surgeon	NAB	NIDR
COPI:	Purvis, Marlene B.	Bio Lab Tech -Animal-	NAB	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project involves Golgi and electron microscopical studies of the synaptic connections of the sensory root of the trigeminal nerve and of the neuronal morphology and organization of the neuropil of the main sensory and spinal trigeminal nuclei. The objectives of these studies are to delineate the trigeminal pain-temperature pathways and to broaden our understanding of oral-facial sensation.

Special Descriptors: None
NIDR Classification: 60210
Total Man Years: 2.25
Professional .75
Other 1.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stephen Gobel	4/18/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-66B-022

Z01 DE 00022-10 LMI B

TITLE OF PROJECT

Phylogenetic Mapping of the Homofermentative Lactic Acid Bacteria

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	London, Jack	Research Microbiologist	LMI	NIDR
COPI:	None			
OTHER:	Chace, Nina M.	Chemist	LMI	NIDR
	Sgorbati, Barbara	Microbiologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Microbiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A second group of evolutionary markers, namely, the glyceraldehyde-3-phosphate dehydrogenases (GAPDH) from Streptococcus faecalis, Periococcus cerevisiae, Lactobacillus acidophilus and Streptococcus mutans, are currently being purified to homogeneity. These enzymes will be used as antigens to prepare GAPDH-specific antisera in rabbits which will subsequently be used to demonstrate structural relatedness among the GAPDHs of homo- and heterofermentative lactic acid bacteria. Results from biochemical and immunological experiments will be used to verify, where possible, and extend the phylogenetic map that was constructed from results of a similar study with the enzyme fructose diphosphate aldolase. The latter study demonstrated that species belonging to the genera, Streptococcus, Pediococcus, Lactobacillus, Acholeplasma, Propionibacterium Eubacterium, Butyribacterium and Aerococcus were derived from a common ancestor; the greater degree of ubiquity of the GAPDH should extend this list to include other genera.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS:	2.25
PROFESSIONAL:	1.00
OTHER:	1.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	for Ch London /C L Hellerqvist	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00024-09 LDBA B

Prev. Ser. No. NIDR-67B-024

TITLE OF PROJECT

Developmental Processes in Genetically Controlled Malformations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Brown, Kenneth S.	Medical Director	LDBA	NIDR
OTHER:	Sederlof, Leena	Visiting Fellow	LDBA	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalie
Section: Connective Tissue
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to describe the development of mutant and inbred animals with genetically produced congenital malformations, particularly those of the oral region, and to examine the interaction between the tissues of these animals in the developmental processes in order to determine the nature of the mechanism producing the genetic defect.

Several methods will be employed. A survey of mouse mutants is being undertaken to examine their oral structures in relation to those of the lines from which they arose. Mutants of specific interest are being collected, and colonies of these animals are to be developed as a basis for experimental study. Timed matings are being made to produce animals of known gestational age. Serial sacrifice and histological study are used to produce documentation of the developmental processes.

Assays of hormonal levels during pregnancy and during teratogenic stimulation are being carried out to evaluate the effects of hormones on development of defects. Teratogenic drugs and dietary restrictions are being studied in specific genotypes of mutant and inbred animals to determine the mechanism of action of the defective genotype.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	41230
TOTAL MAN YEARS:	6.25
PROFESSIONAL:	4.00
OTHER:	2.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Kenneth S. Brown

DATE: 4/23/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-67B-025

Z01 DE 00025-09 LDBA B

TITLE OF PROJECT

In Vitro Synthesis of Collagen and Characterization of the Messenger RNA for Collagen

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Stern, Robert — Medical Officer (Research) — LDBA — NIDR

OTHER: None

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalie
Section: Connective Tissue
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

It is the purpose of this study to synthesize procollagen in cell-free protein synthesizing systems derived from heterologous sources, from animal cells (Krebs II mouse ascites tumor) and from a plant extract (wheat germ). Collagen messenger RNA from chick embryo calvaria (Type I collagen) and mouse chondrosarcoma (Type II collagen) are being examined. This study is divided into several portions.

1. Comparison of ribosomes from various sources in their ability to support collagen synthesis.
2. Search for and fractionation of collagenous tissue specific tRNAs, particularly tRNAs for glycine and proline.
3. Examination of protein synthesizing factors such as collagenous tissue specific initiation factors and their role in translational control of collagen synthesis.
4. Evaluation of the cell-free synthetic collagenous product.
5. Purification and characterization of the collagen specific messenger RNA as to size base composition and oligonucleotide fingerprint pattern following nuclease digestion.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 41211
TOTAL MAN YEARS: 5.75
PROFESSIONAL: 4.75
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert Stern	4/22/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-68B-028

Z01 DE 00028-08 LBS B

TITLE OF PROJECT

Ultrastructure and Cytochemistry of Salivary Glands

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hand, Arthur R.	Senior Dental Surgeon	LBS	NIDR
COPI:	Oliver, Constance	Staff Fellow	LBS	NIDR
OTHER:	Hamosh, Margit			(1)
	Wrathall, Jean			(2)

COOP: (1 & 2) Dept. of Anatomy, Georgetown University, Washington, D. C.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The ultrastructure and cytochemistry of exocrine secretory cells are being studied. Emphasis is being placed upon the basic mechanisms of secretion, with particular attention directed toward the role of the Golgi apparatus and lysosomes in these phenomena. The structure, distribution and cytochemistry of peroxisomes in exocrine glands are also being investigated. The rat parotid gland has been the primary focus of our studies; however, other glands such as the lacrimal, pancreas and thyroid, as well as cultured melanoma cells, are being examined in order to compare them with the parotid gland and to take advantage of cytochemical properties particularly suited for electron microscopy.

The biochemistry, ultrastructure and cytochemistry of developing and adult lingual serous (von Ebner's) glands are also being studied, in order to determine the localization of secretory enzymes, particularly lipase, and the development of the secretory capabilities of the serous cells of the rat tongue.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20216
TOTAL MAN YEARS:	2.25
PROFESSIONAL:	1
OTHER:	1.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Arthur R Hand	4/23/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-68C-029

201 DE 00029-08 CPR C

TITLE OF PROJECT

The effect of school water fluoridation on dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Heifetz, Stanley B.	Dental Director	CPPR	NIDR
COPI:	Horowitz, Herschel S.	Dental Director	CPPR	NIDR
OTHER:	Law, Frank E.	Consultant	OD	NIDR
COOP:	Division of Water Hygiene, Environmental Protection Agency, and Dental Health Division, North Carolina State Board of Health			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In 1968, fluorides were added to the well water supply of a consolidated school (grades 1-12) in Seagrove, North Carolina, at 6.3 ppm, seven times the optimal level recommended for community fluoridation in the geographic area. Children attending the Seagrove School live in an area without a central water supply and where the various drinking waters contain negligible levels of fluoride. Children are exposed to the higher concentration of fluoride at school in an attempt to duplicate the total fluoride intake of children who drink optimally fluoridated water on a full-time basis. Prior to the installation of fluoridation equipment, dental examinations using the DMF surface index were conducted on approximately 1100 children to determine base line caries prevalence. Four-year, follow-up examinations were conducted in May 1972. A brief report containing the four-year findings was presented at the 1973 IADR meeting and the full paper was published in the February 1974 issue of JADA. Follow-up examinations will continue to be conducted at four-year intervals to measure caries-protective benefits as increasingly larger segments of the study population become continuously exposed to fluoridated water at school since entering the first grade. On the eight-year follow-up examinations, an assessment of the prevalence of fluorosis, if any, will be made along with the regular examinations for dental caries.

SPECIAL DESCRIPTORS:	Human, Clinical Trials, Children, Water
NIDR CLASSIFICATION:	10550
TOTAL MAN YEARS:	.7
PROFESSIONAL:	.4
OTHER:	.3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stanley B Heifetz	4/15/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00030-08 DIR A

Prev. Ser. No. NIDR-68A-030

TITLE OF PROJECT

Laboratory Automation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Medlin, Terry P.	Chief, Scientific Appli Unit	OD	NIDR
COPI:	Wilson, John J.	Chief, Data Process & Analysis	OD	NIDR
OTHER:	Coley, Eugene R.	Computer Operator	OD	NIDR
	Zern, Leidy D. Jr.	Electrical Engineering Tech.	OD	NIDR
	Miller, N. Delia	Computer Technician	OD	NIDR
COOP:	Computer Systems Laboratory, Division of Computer Research and Technology, NIH			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Office of the Director
Section: Data Processing Systems & Analysis
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project is a joint collaborative endeavor on the part of NIDR and of the Division of Computer Research and Technology, NIH.

It is a laboratory automation project which is involved in the concurrent on-line acquisition and real time processing of data from a number of analytical instruments and experiments. The project also involves the control of bacteria growth experiments. The computer complex (Honeywell H-316 and H-516) operates under the OLERT multi-programming operating system. The system is interfaced with an amino acid analyzer. liquid scintillation counters, a spectrophotometer, a gas chromatograph, X-ray diffractometer, a fermenter-pumping system and neurophysiology microelectrode experiments. Telecommunication with the NIH central IBM 370 and PDP-10 computers has been established. Extensions this past year have included a neurophysiology laboratory for behavioral studies and a second spectrophotometer. Projected additions include another spectrophotometer, a third neurophysiology laboratory and additional scintillation counters.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	10290
TOTAL MAN YEARS:	3.25
PROFESSIONAL:	.25
OTHER	3.00

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Terry P Medlin

DATE: 5-16 75

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-69A-031

Z01 DE 00031-07 NAB A

TITLE OF PROJECT

Computer Interfacing of Neurophysiologic and Laboratory Instrumentation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Brown, Frederick J. Electronic Engineer (Instru) NAB NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This work involves the development of suitable electronic and electromechanical instrumentation to be used in neuro-physiological and behavioral research. It involves the adaptation and interfacing of these and other instruments to a multipurpose computer installation.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60210
TOTAL MAN YEARS: 1.0
PROFESSIONAL 1.0
OTHER .0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Frederick J Brown	4-16-75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01-DE-00032-07-CPR-A

Prev. Ser. No. 69A-032

TITLE OF PROJECT

Effects of acidulated phosphate-fluoride chewable tablets on dental caries in school children

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Driscoll, William S.	Sr. Dent. Surg.	CP PRNIDR	NIDR
OTHER:	Heifetz, Stanley B.	Dental Director	CP PR	NIDR
	Korts, David C.	Staff Fellow	CP PR	NIDR
	Meyers, Rhea J.	Public Health Analyst	CP PR	NIDR
	Horowitz, Herschel S.	Dent Dir, Chief, CPS	CP PR	NIDR
COOP:	Dental Health Division, North Carolina State Board of Health and the Public Schools of Wayne County, North Carolina			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK - (200 words or less — Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Baseline dental examinations were conducted in September 1969 on approximately 1000 first- and second-grade school children in Wayne County, North Carolina. Children assigned to one test group chew an acidulated phosphate-fluoride (APF) tablet containing 1 mg. F., rinse for 30 seconds with the resulting solution and then swallow the material. Another test group follows the same procedure but, in addition, they repeat the procedure at least 3 hours later with another APF tablet, also containing 1 mg. F. A third group uses a placebo tablet and serves as a control. The treatments are carried out each day in school under supervision of the classroom teacher. Treatments will continue until the respective participants have completed grades six and seven. Follow-up evaluations of the caries preventive effects of the procedures were conducted in April 1972, after 30 months of study, and in May 1974, after 55 months of study. The 55-month examinations also included an assessment for signs of dental fluorosis. A report of the 30-month findings has been published in the July 1974 JADA. A brief report of the 55-month findings was presented at the 1975 AADR meeting and a detailed manuscript of these findings is being prepared for publication. Th next follow-up examinations for dental caries are scheduled for September 1975.

SPECIAL DESCRIPTORS:	Clinical Trials, Children
NIDR CLASSIFICATION:	10550
TOTAL MAN YEARS:	1.25
PROFESSIONAL:	0.80
OTHER:	0.45

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William S. Driscoll	4/15/75

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F Y	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 11-63

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser No. NIDR-69B-034

Z01 DE 00034-07 LMI B

TITLE OF PROJECT

Immunological Mechanisms Involved in Histamine Liberation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hook, William A.	Research Microbiologist	LMI	NIDR
COPI:	Siraganian, Reuben P.	Medical Officer Research	LMI	NIDR
OTHER:	Washington, Julian H.	Biological Lab. Tech. Animal	LMI	NIDR
COOP:	NONE			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Histamine release from mast cells and blood basophils of several different species is studied as one of the immunological mechanisms involved in inflamation. The generation of histamine releasing substance in human serum by microbial cell walls or by antigen-antibody complexes has been studied. This mechanism of basophil activation has been compared with that of IgE-mediated release and found to be differ in several ways. The role of serum factors including complement in the liberation of histamine from human basophils is being studied.

SPECIAL DESCRIPTORS:	Human Blood
NIDR CLASSIFICATION:	20315
TOTAL MAN YEARS:	2.40
PROFESSIONAL:	1.40
OTHER:	1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William A Hook	April 23, 1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01-DE 00035-07 LMI B

Prev. Ser. No. NIDR-69B-035

TITLE OF PROJECT

Activation of B and T Lymphocytes to Produce Lymphokines and Proliferate

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
COPI:	Rosenstreich, David	Medical Officer - Research	LMI	NIDR
OTHER:	Dougherty, Suanne F.	Biologist	LMI	NIDR
	Wahl, Sharon	Staff Fellow	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The reactions of purified B and T cells to mitogens and antigens are being investigated. T cells from agammaglobulinemic chickens proliferate in response to mitogens and produce chemotactic factor. However, in humans both purified T and B cells were found to proliferate in response to appropriate stimulants and make chemotactic factors. These findings have been applied to study patients with periodontal disease. Their T as well as B cells have been found to proliferate and make mediators when stimulated by plaque antigens. These observations suggest a redefinition of the role of B cells in inflammation is required and needs further study.

NIDR CLASSIFICATION: 20314

SPECIAL DESCRIPTORS: 0
TOTAL MAN YEARS: 1.00
PROFESSIONAL: 0.75
OTHER: 0.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Joost J. Oppenheim

DATE: 4/23/73

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00037-06 CPR C

Prev. Ser. No. NIDR-70C-037

TITLE OF PROJECT

The efficacy of an adhesive resin in preventing occlusal caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Horowitz, Herschel S.	Dent Dir, Chief, CPS	CP PR	NIDR
OTHER:	Heifetz, Stanley B.	Dental Director	CP PR	NIDR
COOP:	Dental Division of the Montana State Health Department			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: ~~NIDR, NIH, Bethesda, Maryland 20014~~

SUMMARY OF PROPOSED WORK - *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In May 1970, baseline dental examinations were conducted on 700 grade school children in kindergarten and grades 1, 6 and 7, in Kalispell, Montana, a non-fluoridated community. A total of 450 children were found to have one or more sound pairs of homologous permanent teeth. Only these children were included in the study. One-half of the mouth of each subject was randomly designated as the test side and the other half served as the control side. On the test side, sound occlusal surfaces were conditioned and sealed with the Bis-GMA sealant material developed by Buonocore. Teeth were cleaned in preparation for the sealant by a dental hygienist. Public Health Service dentists did the actual conditioning and application. The physical properties of the sealant including the extent of loss has been evaluated at five, nine, 12, 24, 36 and 48 months after application. Follow-up examinations for dental caries increment have been made after one, two and three years of study. Two-year findings were presented at the 1974 meeting of IADR and have been published in the JADA. Fourth year findings were presented at a symposium on sealants that was part of the 1975 meeting of the AADR. A report containing an overview of findings during the first four years is presently being prepared for publication. Examinations, done five years after the sealants were placed, are scheduled for May 1975.

SPECIAL DESCRIPTORS: Human, Clinical Trials, Children
NIDR CLASSIFICATION: 10530
TOTAL MAN YEARS: 1.0
PROFESSIONAL: .55
OTHER: .45

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Herschel S Horowitz	April 7, 75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 11-63

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-70B-038

Z01 DE 00038-06 LDBA B

TITLE OF PROJECT

Embryological Studies of Facial Development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Johnston, Malcolm C.	Visiting Scientist	LDBA	NIDR
OTHER:	Eto, Kazuhiro	Visiting Fellow	LDBA	NIDR
	Greenberg, Judith	Fellow	LDBA	NIDR

Continued on separate sheet

COOP: (1) Hospital for Sick Children, Toronto
(2) University of Massachusetts
(3) American Dental Association

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalies
Section: Craniofacial Anomalies
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to study the origins, migrations, interactions and derivatives of neural crest and other primordia involved in normal embryological facial development and to use the information for the study of facial malformations. Other aspects of facial development such as primary palate development are also being studied. The normal aspects of the study are conducted primarily on avian and rodent embryos. Extensive use is made of cell, tissue and organ culture procedures. Various histological and biochemical techniques are used. These include radioautography (and other procedures for following the migrations of cells) histochemistry, and column chromatography, as well as interference contrast and electron microscopy. The embryogenesis of spontaneous and induced malformations, particularly cleft lip and palate, is being studied in the mouse. Efforts are being made to influence the abnormal processes leading to "spontaneous" clefts through manipulation of environmental factors.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	41230
TOTAL MAN YEARS:	4.50
PROFESSIONAL:	4.25
OTHER:	.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Malcolm C Johnston	4/22/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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OTHER: Continued

Smuts, Mary Beth	Fellow	LDBA	NIDR
Hazelton, R. D.			(1)
Noden, D. M.			(2)
Steffek, A. J.			(3)

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NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00039-06 CPR A

Prev. Ser. No. NIDR-70A-039

TITLE OF PROJECT

Study of the mode of action of ambient fluoride on the development of dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Larson, Rachel H.	Research Chemist	CP PR	NIDR
OTHER:	Mellberg, James R.			(1)
COOP:	(1) The Kendall Company, Barrington, Illinois			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The ultimate goal of this work is to determine the minimum fluoride exposure associated with maximum caries protection in humans. The rat is being used as the animal model for studying the mode of action of ambient fluoride, which will be provided by a number of experimental procedures.

SPECIAL DESCRIPTION: None
NIDR CLASSIFICATION: 10550
TOTAL MAN YEARS: 2.0
PROFESSIONAL: 1.0
OTHER: 1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Rachel H. Larson	4/21/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-70B-040

Z01 DE 00040-06 NAB B

TITLE OF PROJECT

Activity of Trigeminal Afferent Fibers of the Monkey in Response to Noxious and Innocuous Stimuli

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Dubner, Ronald	Dent Dir, Ch Neurobiol Anesth Br	NAB	NIDR
COPI:	Binck, Joan M.	Biologist	NAB	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Under barbiturate anesthesia, thin nerve bundles are dissected from the infraorbital and inferior alveolar nerves, and their electrical activity recorded and stored on magnetic tape. Thermal and noxious heat stimuli are delivered with a precisely-controlled thermode which has a temperature range of 20°C to 60°C and can produce a temperature change of 10°C at the thermode-skin junction within one second. Data is analyzed with the aid of an on-line, real-time computer system.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60210
TOTAL MAN YEARS: .75
PROFESSIONAL .25
OTHER: .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR

DATE 4/16/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00042-5 LMI B

Prev. Ser. No. NIDR-71B-042

TITLE OF PROJECT

Regulation of Carbohydrate Metabolism in Oral Streptococci

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Chassy, Bruce M.	Research Chemist	LMI	NIDR
COPI:	None			
OTHER:	Palumbo, Emily Victoria	Chemist	LMI	NIDR
	Gibson, Evelyn	Biologist	LMI	NIDR
	Hull, Eunice M.	Biological Aid	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Microbiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK — (200 words or less — Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the biosciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The early stages of the utilization of carbohydrates by oral streptococci are being examined biochemically, physiologically and genetically. Such information provides insight not only into the etiology of carious lesions of the teeth, but also into the evolution of oral bacteria. Attention is focused on sucrases, sucrose transport and subsequent inversion and phosphorylation by specific kinases. Extracellular invertases as well as intracellular glucokinase and fructokinase are being purified and characterized from several strains of Streptococcus mutans. The polysaccharides produced by several isolated glucosyl transferases are being chemically analyzed as well.

A number of strains of oral streptococci are being examined for the presence of plasmids. Preliminary results indicate many strains harbor extrachromosomal DNA. The significance of this finding with respect to the pathogenicity and evolution of these species will be examined.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS:	3.75
PROFESSIONAL:	0.75
OTHER:	3.00

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	B M Chassy/C L Hattenburg	4/23/71

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-71B-043

Z01 DE 00043-05 LMI B

TITLE OF PROJECT

Physiological Studies on Pathogenic Oral Microorganisms

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Donkersloot, Jacob A.	Research Microbiologist	LMI	NIDR
COPI:	DeLeon, Hector A.	Visiting Fellow	LMI	NIDR
	Chassy, Bruce M.	Research Chemist	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Microbiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objective of this study is to provide a physiological basis for the pathogenicity of selected oral microbes. Presently under investigation is the mechanism of glucan formation by Streptococcus mutans.

SPECIAL DESCRIPTORS: 0
NIDR CLASSIFICATION: 10240
TOTAL MAN YEARS: 2.25
PROFESSIONAL: 2.25
OTHER: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jacob A. Donkersloot	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-71A-044

Z01 DE 00044-05 IR A

TITLE OF PROJECT

Handling of Microbial Strain Information by Computers (a)

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Krichevsky, Micah I.	Chief, Microbial Systematics Unit	ODIR	NIDR
OTHER:	Colwell, R. R.			(1)
	Rogosa, M.			(2)
	Donovick, R.			(2)
	Skerman, V.B.D.			(3)
	Socransky, S. S.			(4)
	LaPage, S. P.			(5)
	Fitzgerald, R. J.			(6)

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Unit: Microbial Systematics Unit
Location: c/o American Type Culture Collection
12301 Parklawn Drive, Rockville, Md. 20852

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Microbial strain data are being entered into a data bank with the objective generating a system for providing such services as: data on specific organisms and/or groups of organisms, a locator service for strains with special characteristics, identification of unknown isolates cluster analysis definition of parameters of taxa, data management and report writing aids for research purposes, aids in quality control of tests, methods, and laboratories, and communication of data via common format.

A data file of primary data on a large number of bacteria and yeasts found in the oral cavity and related types is being established. This file will provide a resource for asking both ecological and epidemiological questions of interest in dental research.

Programs are being developed and tested to enter, retrieve, and analyze the data in a variety of ways for epidemiological, diagnostic, taxanomic, ecological etc. uses. The long term goal is to establish a world-wide data bank at a series of cooperating centers.

The system originally developed for bacteria is now being expanded to include the yeasts, molds and protozoa. A series of monographs describing the expanded system is in varying stages of preparation.

(1) Microbiology Department, University of Maryland, College Park, Md.
(2) American Type Culture Collection, Rockville, Md.
(3) University of Queensland, Brisbane, Australia
(4) Forsyth Dental Center, Boston, Massachusetts
(5) Central Public Health Laboratory, London
(6) VA Hospital, Miami, Florida

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Micah I. Krichevsky	5/27/71

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SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 12050, 10110, 20211
TOTAL MAN YEARS : 1.00
PROFESSIONAL : .50
OTHER : .50

☐ Research Grant ☐ Other (Specify)

ENTATIVELY ASSURED AR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-71C-045

Z01 DE 00045-05 LMI C

TITLE OF PROJECT

Contribution of Macrophages to Activation of T and B Lymphocytes and Production of Bone Resorbing Factor

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Oppenheim, Joost J.	Medical Officer - Research	LMI	NIDR
OTHER:	Rosenstreich, David	Medical Officer - Research	LMI	NIDR
	Mergenhagen, Stephan E.	Chief, Lab. of Micro. & Immunol.	LMI	NIDR
	Dougherty, Suanne F.	Biologist	LMI	NIDR
	Weedon, Lynda L.	Biologist	LMI	NIDR
	Wahl, Sharon M.	Staff Fellow	LMI	NIDR

(1)Horton, John E., (2) Raisz, L.

COOP: (1) Walter Reed Army Institute of Research, (2) University of Connecticut Med. School

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The interaction of macrophages with lymphocytes is a prerequisite for antigen-induced stimulation of in vitro lymphocyte proliferation and the production of a variety of mediators such as osteoclast activation factor (OAF) which results in bone resorption. This principle was tested to determine the nature of the OAF producing cells. OAF was found to be produced by lymphocytes, provided macrophages were there to activate them to make it. Furthermore, "OAF-like" activity was also found in the supernatants of long-term "B" lymphoid cell lines.

We have therefore also studied which class of lymphocytes (B or T) macrophages interact with. Macrophages were found to restore the response of purified T but not B lymphocytes, whereas the reaction of both T and B lymphocytes was enhanced in lymphocyte suspensions containing both B and T cells. Therefore, macrophages appear to facilitate the cooperation of T and B cells, but do so by interacting only with T cells. The differences in interaction of T and B receptors with stimulants suggested by these findings are being studied further.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS:	1.50
PROFESSIONAL:	1.00
OTHER:	0.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joost J. Oppenheim per EE.	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev Ser. No. NIDR-71B-046

Z01 DE 00046-05 LMI B

TITLE OF PROJECT

Production of Chemotactic Factors by Guinea Pig B and T Lymphocytes and Their Role in Acute and Chronic Inflammatory Lesions

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wahl, Sharon, M.	Staff Fellow	LMI	NIDR
OTHER:	Kennedy, John B.	Biologist	LMI	NIDR
	McCarthy, James	Biologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Investigations in progress in the Laboratory deal with the isolation of relatively pure populations of T and B lymphocytes which are then studied in vitro for their respective roles in the immune response. Mechanisms of activation of each of these cell types to proliferate and to produce a mediator chemotactic for homologous monocytes are being characterized. Agents capable of activating B cells to produce this mediator include: anti-immunoglobulins, aggregated immunoglobulins, antigen-antibody complexes, polymerized flagellin and endotoxins. Thus, agents interacting with surface receptors activate B cells. This cellular activation may be related to the intracellular levels of cyclic nucleotides (cAMP and cGMP). The correlations between these nucleotides and chemotactic responses are currently under investigation. Finally, glucocorticosteroids have been studied and found to suppress production of chemotactic factors which may explain how these immunosuppressive agents interfere with cellular immune reactions.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	20315
TOTAL MAN YEARS:	2.8
PROFESSIONAL:	0.8
OTHER:	2.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Sharon M. Wahl	4-23-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72A-047

Z01 DE 00047-04 NAB A

TITLE OF PROJECT

Behavioral measurement of pain and temperature discrimination in monkey and human

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Beitel, Ralph E.	Senior Staff Fellow	NAB	NIDR
COPI:	Brown, Frederick J.	Electronic Engineer (Instru)	NAB	NIDR
	Dubner, Ronald	Dent Dir, Ch Neurobiol Anesth Br	NAB	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Monkeys are trained to detect and recognize warming or cooling stimuli applied to their face in order to receive a liquid reward. They are also trained to avoid potentially noxious or escape from noxious stimuli. Measurement of warm, cold, and escape thresholds are made. A corresponding study of pain and temperature thresholds in humans, utilizes the same stimulus parameters.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60214
TOTAL MAN YEARS: 2.0
PROFESSIONAL .75
OTHER 1.25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Ralph E. Beitel

DATE: 4/15/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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National Institute of Dental Research
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00048-04 CIR B

Prev. Ser. No. NIDR-72B-048

TITLE OF PROJECT

Anatomical Studies of the Head of the Newborn Infant

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Bosma, James F.	Chief, Oral Pharyn	CD CIR	NIDR
COPI:	None			
OTHER:	Murayama, Diane R.	Illustrator	CD CIR	NIDR
COOP:	Pierce, Robert, Acting Chair. of Dept. of Radiology, Univ. ILL., Rockford, ILL.			
	Bartner, Howard, Div. of Res. Services, MAPB			
	Mainen, Michael, Private Practice, Minn.			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Invest. & Research Services
Section: Oral Pharyngeal Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This is the sixth year of gross anatomical studies of the face, pharynx and cranium of the human fetus at term. An Atlas of Cranial Anatomical and Radiographic Sections of the Infant Cranium authored by Robert Pierce (former associate in Radiology at the Clinical Center), Michael M. Mainen (former Clinical Associate in this Section) and James F. Bosma has been submitted for commercial publication.

Current anatomical description and related illustrations of the newborn's lower pharynx and larynx will complete the material for a general anatomy book on the head of the newborn infant, excepting the brain.

SPECIAL DESCRIPTORS:	Developmental anatomy, Tomography, Cranium, Mouth, Pharynx, Larynx
NIDR CLASSIFICATION:	41420, 41430
TOTAL MAN YEARS:	1.5
PROFESSIONAL:	.5
OTHER:	1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James F. Bosma	4-23-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72B-049

NIDR- Z01 DE 00049-04 LB B

TITLE OF PROJECT

Comparative Aspects of the Mamalian Transglutaminases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI :	S. I. Chung	Research Chemist, LB, NIDR
OTHERS:	J. E. Folk	Chief, Enzyme Chem. Sec., LB, NIDR
	S. Y. Lee	Visiting Fellow, LB, NIDR

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section : Enzyme Chemistry
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

As an extension of a project carried out over the past few years, studies will be continued on the isolation and characterization of an important group of enzymes termed transglutaminases that catalyzed the formation of covalent cross-links between protein molecules. Three distinct classes of these enzymes in guinea pig and human tissues and organs have been defined in this laboratory. The isozymic nature of these enzymes is under investigation. The presence of high concentrations of a transglutaminase in red blood cells of human and guinea pig is under further study. Of particular interest are the roles of the individual transglutaminases in blood coagulation, wound healing, seminal plasma coagulation during fertilization, cell membrane formation, cross-linking of hair proteins, keratin formation, and covalent attachment of biological amines in protei

Biological control mechanisms, essential metal ion requirements, the immunochemical and the structural aspects of zymogen activation, active site and substrate specificities are under investigation. The biosynthesis, degradation and hormonal regulations of plasma protransglutaminase are currently under investigation.

SPECIAL DESCRIPTORS:	Blood
NIDR CLASSIFICATION:	20325
TOTAL MAN YEARS :	3.25
PROFESSIONAL :	1.75
OTHER :	1.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	S. I. Chung	5-2-75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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Not for publication or publication reference.

U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72B-050

Z01 DE 00050-04 LMI B

TITLE OF PROJECT

Extracellular Polysaccharide Synthesis of Caries Producing Streptococci

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Ciardi, Joseph E.	Senior Staff Fellow	LMI	NIDR
COPI:	Wittenberger, Charles L.	Chief, Microbiology Section	LMI	NIDR
OTHER:	Hageage, George	Research Microbiologist	LMI	NIDR
	Bowen, William	Visiting Scientist	CPR	NIDR
	Beaman, Alfred	Microbiologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Microbiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK — *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The extracellular Glucans of Streptococcus mutans are involved both in the adhesive interactions among these organisms and in their colonization of the tooth surface. The mechanisms by which these polysaccharides are synthesized and the nature of their chemical structure, therefore, are being actively studied. The constitutive extracellular glucan synthesizing system (Glucosyltransferases) of S. mutans 6715 has been extensively purified. The purified system has been resolved into two major enzyme components (making either water soluble or insoluble products), each of which contains several catalyzically active glycoprotein species. The interaction of these enzyme species in glucan formation and their glycoprotein nature are under investigation. Various inhibitors of glucan formation are being sought as an approach to the effective prevention of microbial colonization of the tooth surface. The feasibility of using purified glucosyltransferase preparations in a vaccine against dental caries is also being studied. The enzyme systems of the five different Bratthall serotypes of S. mutans have been characterized and compared both immunologically and biochemically. Studies in animal models are now in progress.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS:	2.5
PROFESSIONAL:	1.5
OTHER:	1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joseph E. Ciardi	4/23/75

DO NOT WRITE BELOW THIS LINE — FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

PROJECT DISCONTINUED

The project originally assigned to

this page has been discontinued.

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00055-04 LMI B

Prev. Ser. No. NIDR-72B-055

TITLE OF PROJECT

Transport and Metabolism of Hexitols in Streptococcus mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Maryanski, James H.	Staff Fellow	LMI	NIDR
COPI:	Wittenberger, C. L.	Chief, Microbiology Section	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Microbiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The transport of mannitol in Streptococcus mutans by a phosphoenolpyruvate-dependent phosphotransferase system has been demonstrated, and the properties of this enzyme system are being studied in relation to similar transport systems reported for other bacteria. Mutants of Streptococcus mutans unable to grow on mannitol are being studied to elucidate the enzymatic reactions involved in hexitol transport and metabolism. The effect of various metabolic intermediates on the regulation of the phosphotransferase system and on mannitol-1-phosphate dehydrogenase is currently under investigation.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS :	1.25
PROFESSIONAL :	1.25
OTHER :	0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James H Maryanski	4/23/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72A-056

Z01 DE 00056-04 DIR A

TITLE OF PROJECT

Neurophysiology Software

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Medlin, Terry P.	Chief, Scientific Appli Unit	OD	NIDR
COPI:	Robinson, Merle S.	Computer Programmer	OD	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Office of the Director
Section: Data Processing Systems and Analysis
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

1. MULTIPROGRAMMING Systems Software for the NIDR Laboratory Automation System: enhancements to allow growth with increased reliability and alterations to improve speed performance and increase flexibility.

2. Development of statistical packages for analysis of neurophysiology data.

3. Development of a data base management system to save, migrate, format, and retrieve data.

4. Development of on-line, real-time software to run behavioral experiments without researcher intervention.

5. Development of improved interactive graphics techniques for visual presentation of histograms.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	10290
TOTAL MAN YEARS:	1.25
PROFESSIONAL	.50
OTHER	.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Terry P. Medlin	5-16-75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72B-058

Z01 DE 00058-04 LMI B

TITLE OF PROJECT

Contribution of Nuts and Corn Mitogens to Gingival Inflammation

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Radentz, William	Guest Worker	LMI NIDR
OTHER:	Oppenheim, Joost J.	Medical Officer - Research	LMI NIDR
COOP:	None		

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Periodontists have observed a significant incidence of "sterile" gingival abscesses that contain corn husks. The possibility of a causal relationship between the pathogenesis of this gingival inflammation and impacted food particles is being studied. Saline extracts of a variety of nuts and corn have therefore been tested and found to be mitogenic for lymphocytes, to stimulate the production of factors chemotactic for macrophages and to release histamine from basophiles of allergic subjects. The likelihood that some foods can directly cause tissue inflammation by nonspecific mitogenic activation of lymphocytes is being further studied.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS:	0.75
PROFESSIONAL:	0.75
OTHER:	0

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William Radentz	4/23/72

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72B-060

Z01 DE 00060-04 LMI B

TITLE OF PROJECT

The Mechanism of Action of Lymphocyte Stimulation of Bacterial Endotoxins

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Rosenstreich, David	Medical Officer - RESEARCH	LMI	NIDR
OTHER:	Mergenhagen, Stephan E.	Chief, Lab. of Micro. & Immunol.	LMI	NIDR
	Weedon, Lynda L.	Biologist	LMI	NIDR
	Glode, L. Michael	Research Associate	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Previous work demonstrated that a purified bacterial glycolipid was mitogenic for lymphocytes. We have now found that a purely synthetic glycolipid, is also mitogenic. It is now possible to synthesize glycolipids with specific functional endotoxin-like properties but without other deleterious properties.

The ability of mouse lymphocytes to respond to endotoxin has been found not to depend on prior sensitization since cells from germ-free mice respond as well as those from conventionally reared animals.

The mouse lymphocytes response to endotoxin is under genetic control. Endotoxin responsiveness is controlled by an autosomal dominant gene in C3H/HeJ mice and by a sex-linked recessive gene in CBA/HN mice. The inability of mouse cells to respond to endotoxin in vitro has been found to correlate with certain in vivo activities of endotoxin such as LPS lethality.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS:	1.50
PROFESSIONAL;	.50
OTHER:	1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David Rosenstreich	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00061-04 LMI B

Prev. Ser. No. NIDR-72B-061

TITLE OF PROJECT

Complement Activation and its Relationship to the Inflammatory Response

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sandberg, Ann L.	Research Biologist	LMI	NIDR
OTHER:	Phillips, Jean, J.	Biologist	LMI	NIDR
	Liebrecht, Georgiana	Microbiologist	LMI	NIDR
	Mergenhagen, Stephan, E.	Chief, Lab. of Micro. & Immunol.	LMI	NIDR
COOP:	Raisz, Lawrence G.			(1)

(1) University of Rochester, Rochester, N.Y.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Humoral Immunity
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The mechanism by which complement activation at a cell surface results in prostaglandin synthesis and concomitant bone resorption in organ cultures is currently under investigation. This process appears to be dependant on immunoglobulins with a specificity for cell surface antigens and can be initiated by either the classical or alternative complement pathways. The interaction of the different immunoglobulin classes with the complement system and the influence of antigenic structure on the mode of complement interaction are under examination.

SPECIAL DESCRIPTORS: 0
NIDR CLASSIFICATION: 20315
TOTAL MAN YEARS: 2.4
PROFESSIONAL: 0.8
OTHER: 1.6

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Ann L Sandberg	4/23/

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

PHS-166
REV. 5-70

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: NIDR-72-B-063

Z01 DE 00063-04 CPR B

TITLE OF PROJECT

Occurrence of Oral Streptococci in the oral cavity and feces of children

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Stiles, H. M. Microbiologist
OTHER: None
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section : Etiology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A study of sample parameters for a longitudinal investigation of the first appearance and subsequent prevalence of oral streptococci in children has been completed. The oral and fecal samples collected from approximately 250 children have been examined for the presence of Streptococcus mutans. Every S. mutans isolate has been further subjected to serotyping by two methods.

Special Descriptors: Human, Children
NIDR Classification: 10120
TOTAL MAN YEARS: .35
PROFESSIONAL : .35
OTHER : .0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H M Stiles	3/12/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72A-064

Z01 DE 00064-04 CPR A

TITLE OF PROJECT

Identification of S. mutans and other dental plaque Streptococci using cultural, biochemical and immunological methods.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Thomson, L. Ariel	Senior Dental Surgeon	CP PR	NIDR
COPI :	Brunelle, Janet Ann	Statistician - Health	CP PR	NIDR
	Facklam, Richard	Microbiologist		(1)
	Cherry, William	Microbiologist		(2)
	McKinney, Roger	Biochemist		(3)
COOP :	(1) (2) (3) Center for Disease Control, Atlanta, Georgia			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of the present project is to provide identification criteria (with supporting data) for certain streptococci considered to be potentially cariogenic. In addition, the immunofluorescent capabilities of several laboratories have been joined in collaborative research designed to develop FA reagent grade conjugates specific for certain plaque streptococci.

Numerical taxonomic methods, other computer techniques, as well as conventional methods are being used to analyze the data from over 700 strains to develop differentiating criteria. Colored plates are being prepared to portray representative colonial types.

Efforts in fluorescent antibody research have resulted in the development of improved immunization schedules, higher titered antisera, the optimal F/P ratio for conjugates and major advances in immunoabsorption methods to improve the specificity of S. mutans conjugates. A new column serum fractionation method and EDTA-Cellulose-Bacterial Column absorption have been developed. Improved methods for labeling conjugates with rhodamine have been developed.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS:	2.6
PROFESSIONAL:	.6
OTHER:	2.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	L Arnold Thomson	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-72C-065

Z01-DE-00065-04 CIR C

TITLE OF PROJECT

Clinical Evaluation of a New Type of Dental Radiographic System

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Webber, Richard L.	Dental Director	CD CI	NIDR
COPI:	Nagel, Roger	Computer Research Scientist	CD CI	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A new type of radiographic system which couples an intraoral source of radiation to an extraoral transducer is to be tested clinically. The output of the device included both conventional and Polaroid type radiographic displays. The latter are available seconds after exposure. The design provides for the production of images with far less radiation than required by conventional techniques.

Factors to be evaluated include task specificity, practical constraints, patient acceptance, training requirements, and diagnostic quality. Diagnostic performance is to be determined from radiographs of phantoms containing known pathology and the results are to be compared with comparable data produced conventionally.

Developmental efforts include computer simulation of specific components and clinical demonstration of new collimating and beam-directing capabilities.

NIDR CLASSIFICATION:	10400
TOTAL MAN YEARS:	.75
PROFESSIONAL:	.30
OTHER:	.45

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Richard L. Webber

DATE: 4/17/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR 72C-066

Z01-DE-00066-04 CIR C

TITLE OF PROJECT

Determination of Task-Specific Factors Influencing Diagnostic Performance from Radiographs

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Webber, Richard L.	Dental Director	CD CI	NIDR
COPI:	Nagel, Roger	Computer Research Scientist	CD CI	NIDR
OTHER:	None			
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Research is being directed toward the determination of factors limiting diagnostic performance from dental radiographs. Of specific interest, is the consideration of task-specific questions from the point of view of information theory.

Specific experiments involve selective manipulation of factors known to reduce the information capacity of radiographic displays and the determination of the effects (if any) on diagnostic performance by human interpreters. This approach permits specificati of diagnostically meaningful information in terms of spatial frequency spectra found to be essential for specific diagnostic tasks.

Current efforts include modeling the effects of pertinent variables in a complete radiographic system in order to specify the influence of variations in spectral sensitivity of the detector, alterations in beam geometry, changes in the energy distribution of the primary beam, etc.

NIDR CLASSIFICATION:	10400
TOTAL MAN YEARS:	.75
PROFESSIONA:	.50
OTHER:	.25

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR

DATE 4/17/72

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

PHS-166
REV. 5-70

Prepared for the Science Information Exchange.

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-73B-067

Z01 DE 00067-03 LMI B

TITLE OF PROJECT

Studies on Polysaccharides Produced by Oral Streptococci and Actinomycetes

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Bladen, Howard A.	Research Microbiologist	LMI	NIDR
COPI:	None			
OTHER:	Hassell, Florence	Biologist	LMI	NIDR
	McCabe, Robert	Biological Lab. Tech.	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology & Immunology
Section: Microbiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The addition of dextran plus sucrose to cell-free culture supernatants of Streptococcus mutans resulted in the formation of a semi-solid gel closely resembling 2% agar. This phenomenon is dependent upon an extracellular factor(s) which is referred to as "gel factor" (GF). The GF is produced by cells grown in complex medium with glucose, maltose or fructose as the primary energy source. GF appears to be protein in nature; it is heat labile and is inactivated by trypsin. The GF is produced by S. mutans strains belonging to Bratthall's group "d" but not by strains belonging to group "a", "b" or "c". The potential role of this factor and its product in colonization and cell adhesion is being assessed.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	10240
TOTAL MAN YEARS:	3
PROFESSIONAL:	1
OTHER:	2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Howard A. Bladen	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-73B-068

Z01 DE 00068-03 LBS B

TITLE OF PROJECT

The Reactivity of Phosphorofluoridate with Calcium Phosphate Salts

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Eanes, Edward D. Chief, Molecular Structure Section, LBS NIDR
COPI: None
OTHER: None
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The chemical interaction of phosphorofluoridate (PO_3F^{2-}) with amorphous calcium phosphate (ACP) and crystalline apatite (CA) is being studied. The extent of PO_3F^{2-} adsorption on ACP and CA, the stability of adsorbed PO_3F^{2-}, and the inhibition of adsorption by other anionic species are being investigated. PO_3F^{2-} reactivity will be correlated with the composition, texture and prior chemical history of ACP and CA.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10220
TOTAL MAN YEARS: 1
PROFESSIONAL: .25
OTHER: .75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

National Institute of Dental Research

SIGNATURE OF PRINCIPAL INVESTIGATOR

Edward D. Eanes

DATE

4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-73c-070

Z01 DE-00070-03 CPR C

TITLE OF PROJECT

Evaluation of a combination of self-administered measures of fluoride exposure for control of dental caries in a non-fluoride area

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Horowitz, Herschel S.	Dent Dir, Chief, CPS	CP PR	NIDR
OTHER:	Heifetz, Stanley B.	Dental Director	CP PR	NIDR
	Meyers, Rhea	Public Health Analyst	CP PR	NIDR
	Driscoll, William S.	Sr. Dental Surgeon	CP PR	NIDR
COOP:	Virginia Department of Health, Division of Dental Health and Albemarle-Charlottesville-Nelson Health District, and Nelson County Public School System			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK - *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Base line dental examinations were conducted in October 1972, on approximately 2200 first- through twelfth-grade children in Nelson County, Virginia. All study participants in grades 1-6 chew daily in school under supervision of the classroom teacher an acidulated phosphate-fluoride (APF) tablet containing 1 mg. F, rinse for 30 seconds with the resulting solution and then swallow the material. Once a week in school the same children also swish 10 milliliters of a 0.2 percent sodium fluoride solution for 60 seconds and then empty the contents of the mouth into a cup. A fluoride-containing dentifrice is distributed to the same children for use at home, and they receive toothbrushes periodically to take home. County health authorities and the county public school system are responsible for developing an oral health education program designed for elementary grades. These combined preventive procedures will continue in the elementary schools for a minimum of ten years. Follow-up dental examinations are carried out biennially in all schools. The first follow-up survey was done in October 1974. Data are presently being analyzed.

SPECIAL DESCRIPTORS:	Human, Clinical Trial, Children
NIDR CLASSIFICATION:	10540
TOTAL MAN YEARS:	1.75
PROFESSIONAL:	1.25
OTHER:	0.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Herschel S. Horowitz	April 15, 1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01-DE-00071-03-CPR-C

Prev. Ser. No.: 73C-071

TITLE OF PROJECT

Evaluation of a combined program of school water fluoridation and sodium fluoride mouthrinsing for the control of dental caries

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Suomi, John D.	Project Scientist	CP PR	NIDR
OTHER:	Meyers, Rhea	Public Health Analyst	CP PR	NIDR
	Satterfield, William and Murphy, Richard			(1)
COOP:	(1) North Carolina State Board of Health, Fayetteville and Greenville, N.C., respectively			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Community Programs
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK - *(200 words or less — Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

About 2500 children attending grades 1 through 12 at three schools in Robeson County, North Carolina, are exposed to 1) fluoridation of the school water supply at four and one-half times the level estimated to be optimum for community fluoridation in the same geographic areas, and 2) weekly mouthrinsing with 0.2% NaF solution. Teachers dispense 10 millimeters of solution to each participant-child and supervise the one-minute rinsing procedure which is carried out in the classroom. To evaluate the long-term benefits of the combined treatments on the prevalence of dental caries, pre-treatment clinical data will be compared with the data obtained every two years until the completion of the program in 1984. Base line examinations using the DMF tooth and surface index were conducted in September 1972. Follow-up examinations were made in November/December, 1974. The project is currently in its third year.

SPECIAL DESCRIPTORS:	Human, Clinical Trial, Children, Water
NIDR CLASSIFICATION:	10540
TOTAL MAN YEARS	1.1
PROFESSIONAL	0.6
OTHER:	0.5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John D. Suomi	4/15/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 11-63

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-73B-073

Z01 DE 00073-03 LBS B

TITLE OF PROJECT

X-ray Diffraction Studies of Bone Mineral in Human Disease

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Termine, John D.	Research Biochemist	LBS	NIDR
COPI:	None			
OTHER:	Avioli, L. V.			(1)
	Russell, J. R.			(2)

COOP: (1 & 2) Jewish Memorial Hospital, Washington U. School of Medicine, St. Louis, Mo.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Hydrazine extraction is used to prepare bone mineral specimens that are both free of protein and unaltered in physicochemical properties compared to native tissue. The deproteinated bone specimens are then examined by quantitative x-ray diffraction procedures measuring diffraction intensity and broadening. Conventional diffraction equipment is automated and computerized in order to time-average these data. The x-ray diffraction measurements accurately estimate both the quantity and average size (and/or perfection) of the apatite present in the biological specimen relative to synthetic standards of similar composition and crystal texture. Thus, the relative level of average mineral maturation is assessed for each deproteinated bone sample examined. These experimental procedures are being used to study bone degeneration and recovery in chronic uremia, with emphasis placed on the effectiveness of various methods of treatment for this disease.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20324
TOTAL MAN YEARS:	.75
PROFESSIONAL:	.25
OTHER:	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
ational Institute of Dental Research	John D Termine	4/3/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00074-03 LBS B

Prev. Ser. No. NIDR-73B-074

TITLE OF PROJECT

Physicochemical Studies of Protein-Mineral Interactions

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Termine, John D. — Research Biochemist — LBS — NIDR

COPI: None

OTHER: Peckauskas, R. (1)
Pullman, I. (2)

COOP: (1 & 2) Department of Radiology, New York Medical College, New York, N. Y.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The structural and kinetic interaction of mineral ions and mineral solids with synthetic and biological macromolecules and metabolites is being studied by a number of physicochemical techniques including infrared spectroscopy, laser Raman spectroscopy, electron paramagnetic resonance spectroscopy and x-ray diffraction. The mineral ions encompass the alkaline earth metals and the HPO_4^{-2}, $H_2P_2O_7^{-2}$ and HCO_3^- anions, while the mineral solids include the synthetic amorphous and apatite calcium phosphates. The macromolecules include cationic, neutral and anionic proteins, both simple and complex, as well as model mono- and polyfunctional biopolymers. Macromolecular entropic, electrostatic and conformational influences on mineral ion/solid binding are under study. Mineral solid-protein fiber quaternary structure relationships are also being investigated as well as the alterations in this relationship induced by non-fibrous tissue protein components.

NO1-DE-32418

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 20324
TOTAL MAN YEARS: 1.75
PROFESSIONAL: .75
OTHER: 1.00

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research		4/3/75

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Previous Serial No. NIDR-73C-075

Z01 DE 00075-03 LOM C

TITLE OF PROJECT

Baseline Studies of the Effect of Pilocarpine on Parotid Gland Function in Sjögren's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wolf, Robert O.	Dental Director	LOM	NIDR
COPI:	None			
OTHER:	Chused, Thomas M.	Sr. Staff Fellow	LMI	NIDR
	Kassan, Stuart S.	Clinical Associate	LMI	NIDR
	Johnston, Gerald S.			(1)
COOP:	(1) Nuclear Medical Department, Clinical Center, NIH			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The therapeutic effect of pilocarpine on xerostomia of Sjögren's syndrome will be examined. Affected individuals will be compared to control individuals before and after a short course of pilocarpine therapy. Parotid gland function and saliva quality will be monitored by sialometry, scintigraphy and chemical analysis of the secretion.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	10400
TOTAL MAN YEARS:	.25
PROFESSIONAL:	.25
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert O. Wolf	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74A-077

Z01 DE 00077-02 CPR A

TITLE OF PROJECT

Factors influencing Transmission of S. mutans in the young rat

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Amsbaugh, Suzanne	Biologist	CP PR	NIDR
OTHER:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
COOP :	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this study is to determine the earliest transmission of S. mutans to the young rat nursed by a mother infected with S. mutans and fed a supporting diet. Special attention will be given to the effect of such factors as age of animal, tooth development and variations in the diet.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10120
TOTAL MAN YEARS: 0.2
PROFESSIONAL: 0.1
OTHER: 0.1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Suzanne M Amsbaugh	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-078

Z01 DE 00078-02 NAB B

TITLE OF PROJECT

Light and electron microscopic observations of oral-facial skin receptors in the monkey

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Binck, Joan M.	Biologist	NAB	NIDR
COPI:	Gobel, Stephen	Sr Dental Surgeon	NAB	NIDR
	Dubner, Ronald	Dent Dir, Ch Neurobiol Anesth Br	NAB	NIDR
OTHER:	Munger, Bryce			(1)
COOP:	(1) Hershey Medical Center, Hershey, Pennsylvania			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Oral-facial skin receptors, identified with physiological techniques, are studied histologically. Light and electron-microscopic techniques are utilized to study the morphological characteristics of nerve terminals activated by mechanical stimulation. Work has been completed on those receptors associated with non-sinus hairs, and is continuing on those associated with sinus hairs. An attempt will be made to correlate these anatomical observations with the physiological characteristics of these receptors.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60210
TOTAL MAN YEARS: .75
PROFESSIONAL .25
OTHER .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joan M. Binck	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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National Institute of Dental Research

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74A-079

Z01 DE 00079-02 CIR A

TITLE OF PROJECT

Conferences and Publication of Symposia

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Bosma, James F.	Chief, Oral Pharyn	CD CIR	NIDR
COPI:	Weiffenbach, James M.	Senior Staff Fellow	LMI	NIDR
OTHER:	None			
COOP:	Fogarty International Center National Institute of Child Health and Human Development			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Section: Oral Pharyngeal Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The Fourth Symposium on Oral Sensation and Perception: Development in the Fetus and Infant, November, 1972, under the auspices of the NIDR and the Fogarty International Center, Editor: James F. Bosma, was off the press, Government Printing Office, in June, 1974. To our surprise, the supply (1000 copies) reserved for sale by the Superintendent of Documents is now expended, and the book is "out of print". We hope to arrange a reprinting.

A Symposium on Development of Upper Respiratory Anatomy and Physiology, in Relation to Sudden Infant Death, April, 1974, under auspices of the NIDR, the National Institute of Child Health and Human Development, and the Fogarty International Center, has been accepted for commercial publication. Editors: James F. Bosma and Jane Showacre.

A Symposium on Development of Preference for Sweet Taste, June, 1974, under the auspices of the NIDR and the Fogarty International Center is pending publication by the Government Printing Office. Editor: James M. Weiffenbach.

SPECIAL DESCRIPTORS:	Children, Human
NIDR CLASSIFICATION:	41323
TOTAL MAN YEARS:	1.5
PROFESSIONAL:	.5
OTHER:	1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James F. Bosma	Apr-235

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-080

Z01 DE 00080-02 LOM B

TITLE OF PROJECT

Virus-induced Diseases of the Endocrine and Exocrine Glands

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Yoon, Ji-Won	Staff Fellow	LOM	NIDR
COPI:Chairez, Ruben	Guest Worker	LOM	NIDR
COPI:Notkins, Abner Louis	Medical Director, Chief of	LOM	NIDR
OTHER: Fierverker, Alan S.	Microbiologist	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The development of a diabetes-like syndrome in mice by the M-variant of encephalomyocarditis (EMC) virus seems to depend on the function of beta cells as well as alpha cells. Thus, the correlation between EMC-virus multiplication and beta cell degranulation and degeneration is being studied in vitro and in vivo. Further, the relationship between the release of insulin and multiplication of virus in the pancreatic beta cells will be studied in vitro. In addition, genetic factors that may play a role in the development of diabetes is being studied in the mice of F_1 and F_2 generation.

SPECIAL DESCRIPTORS: DIABETES
NIDR CLASSIFICATION: 33500
TOTAL MAN YEARS: 4.70
PROFESSIONAL: 2.20
OTHER: 2.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		4/24/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00081-02 CPR A

Prev. Ser. No. NIDR-74A-081

TITLE OF PROJECT

Development of an Anti-caries Vaccine

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Bowen, William H.	Visiting Scientist	CP RB	NIDR (1)
OTHER:	Delgard, Daniel			
COOP:	(1) Hazleton Laboratories			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A colony of young monkeys of the species Macaca fascicularis has been established in Hazleton Laboratories. They were inspected by a vetinary surgeon before being dispatched from Malaysia. They have been subjected to intensive quarantine procedures including tuberculin testing. Antibiotics such as tetracycline have been avoided. Pre-experimental samples of plaque have been obtained from all animals. Strep. mutans has not been found. The biochemical analysis of plaque suggest that its composition is similar to that found in man. The levels of serum immunoglobulins have been determined in all animals. Wide variations have been found. The animals have been divided into experimental groups on the basis of age and the levels of immunoglobulins. The monkeys are now on an experimental regimen.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10570
TOTAL MAN YEARS:	1.5
PROFESSIONAL:	.5
OTHER:	1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William H Bowen	4/28/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-083 Z01 DE 00083-02 LOM B

TITLE OF PROJECT

Immune Responses to Herpes Simplex Infection

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Burns, William H.	Research Associate	LOM	LOM	NIDR
COPI: Notkins, Abner Louis	Medical Director, Chief of	LOM	LOM	NIDR
OTHER Billups, Lloyd	Biologist	LOM	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine,
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Mice are depleted of thymus-dependent immune responses by thymectomy, lethal irradiation with bone marrow reconstitution, and anti-lymphocyte sera. This results in increased susceptibility of the mice to herpes infection. Restoration of resistance by reconstitution of the mice with selected subpopulations of T-lymphocytes is being attempted to determine which lymphocytes are active in conferring resistance to this infection.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 31300
TOTAL MAN YEARS: 3.50
PROFESSIONAL: 1.00
OTHER: 2.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William H Burns	4/24/7-

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00084-02 LMI B

Prev. Ser. No. NIDR-74B-084

TITLE OF PROJECT

Autoimmunity in New Zealand Mice

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Chused, Thomas M.	Medical Officer Research	LMI	NIDR
COPI:	Kassan, Stuart S.	Clinical Associate	LMI	NIDR
OTHER:	Brown, Elinor	Biologist	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objective of this project is to determine the etiology of autoimmunity in New Zealand mice. Endogenous activation of suppressing T cells is being studied. Genetic studies of the factors producing autoimmune disease are being performed.

SPECIAL DESCRIPTORS:
NIDR CLASSIFICATION: 34000
TOTAL MAN YEARS: 2.50
PROFESSIONAL: 1.50
OTHER: 1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M. Chused M.D.	4-23-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-085

Z01 DE 00085-02 LMI C

TITLE OF PROJECT

Studies in Sojogren's Syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Chused, Thomas M.	Medical Officer Research	LMI	NIDR
COPI:	Kassan, Stuart S.	Clinical Associate	LMI	NIDR
OTHER:	NONE			
COOP:	NONE			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The extra salivary complications lymphocyte abnormalities HL-A types, dental sequallae, presence of viruses and therapy are being investigated.

SPECIAL DESCRIPTORS:
NIDR CLASSIFICATION: 34000
TOTAL MAN YEARS: 0.50
PROFESSIONAL: 0.50
OTHER:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Thomas M. Chused M.D.	4-23-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

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Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00086-02 LOM C

Prev. Ser. No. NIDR-74C-086

TITLE OF PROJECT

Treatment of Aphthous Stomatitis

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Graykowski, Edward A.	Medical Director	LOM	NIDR
COPI:	None			
OTHER:	Senning, Rickley	Chief, Biometry Sec.	CPR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Therapeutic trials of steroids and tetracyclines will be carried out to assess effectiveness in treatment of aphthous stomatitis. This will be done in a double-blind manner, and results compared to placebo therapy.

SPECIAL DESCRIPTORS: Clinical Trials, Human
NIDR CLASSIFICATION: 32400
TOTAL MAN YEARS: 1.00
PROFESSIONAL: .50
OTHER: .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Edward A. Graykowski	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-087

Z01 DE 00087-02 LMI B

TITLE OF PROJECT

In Vitro Culture of Human Basophils

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Drobis, Jeffery	Clinical Associate	LMI	NIDR
COPI:	Siraganian, Reuben P.	Medical Officer Research	LMI	NIDR
OTHER:	NONE			
COOP:	NONE			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Mechanisms involved in the generation of histamine and antigen receptors by the peripheral human basophil are under investigation using an in vitro cell culture system.

SPECIAL DESCRIPTORS: Human Blood
NIDR CLASSIFICATION: 20315
TOTAL MAN YEARS: 0.70
PROFESSIONAL: 0.70
OTHER: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Jeffrey Drobis	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-088

Z01 DE 00088-02 LBS B

TITLE OF PROJECT

Chemical, Structural, and Morphological Studies on the Interaction of Apatitic Substrates with Calcium Phosphate Solutions.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Eanes, Edward D. Chief, Molecular Structure Section LBS NIDR
COPI: None
OTHER: None
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Molecular Structure
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The interaction of aqueous solutions of calcium and phosphate ions with apatitic substrates is being studied. Parameters being investigated are the rate and extent of the interchange of ionic calcium and phosphate between solution and substrate, and the effects this interchange has on substrate morphology and structure. Particular attention is being directed to the mechanisms by which new material is accreted onto the apatitic substrate under conditions of solution supersaturation. The effect on apatite crystals of rapid, cyclical alterations in solution conditions such as can be affected by sudden pH changes is also being studied, as is the role of inorganic and bioorganic adducts in modifying the above parameters. The purpose of these studies is to establish the fundamental physicochemical mechanisms by which enamel apatite responds to changes in oral fluid environment.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10220
TOTAL MAN YEARS: 2.5
PROFESSIONAL: .75
OTHER: 1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Edward D Eanes	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-089

Z01 DE 00089-02 CIR C

TITLE OF PROJECT

The Application of the NBT Test in Evaluating Transient Dental Bacteremia

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sweet, James B.	Sr. Dental Surgeon	CD CIR	NIDR
COPI:	Chusid, Michael J.	Clinical Associate	LCI	NIAID

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Serial NBT tests are performed on patients undergoing oral surgical procedures. The data will be evaluated to determine if the NBT test can detect acute bacteremia. Parallel cultural studies will be utilized comparatively to test the accuracy of the NBT test.

SPECIAL DESCRIPTORS: Human, Blood
NIDR CLASSIFICATION: 20313
TOTAL MAN YEARS: 1.0
PROFESSIONAL: 0.5
OTHER: 0.5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		April 18, 197

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00091-02 LOM C

Prev. Ser. No. NIDR-74C-091

TITLE OF PROJECT

Investigations on the Etiology of Oral Mucosal Ulcerations

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Graykowski, Edward A.	Medical Director	LOM	NIDR
COPI:	None			
OTHER:	John J. Hooks	Sr. Staff Fellow	LOM	NIDR
	Charles Daniels			(1)
COOP:	(1) Duke University, Durham, North Carolina			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project is concerned with the etiology of oral ulcerations produced by - 1) primary and recurrent herpes, 2) recurrent aphthous ulcers. The objectives of the project are: (1) To establish the salient clinical features of these diseases for differential diagnosis; (2) to establish the histopathologic aspects of the oral ulcerations; (3) to establish the role of predisposing factors in the etiology of these diseases; (4) to investigate the mechanism which governs recurrence; (5) to establish the use of laboratory procedures as an aid in diagnosis; (6) to identify and characterize the etiologic agent(s) and histopathologic mechanism in these diseases.

SPECIAL DESCRIPTORS: Human, Clinical Trials
NIDR CLASSIFICATION: 32200
TOTAL MAN YEARS: .60
PROFESSIONAL: .60
OTHER: .00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED

SIGNATURE OF PRINCIPAL INVESTIGATOR: Edward A. Graykowski

DATE: 4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DA

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-094

Z01 DE 00094-02 LOM B

TITLE OF PROJECT

Aphthous Ulcers and Dermatologic Disorders

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hooks, John J.	Senior Staff Fellow	LOM	NIDR
COPI:	Notkins, Abner L.	Medical Director, Chief, LOM	LOM	NIDR
OTHER:	Geis, Shirley	Microbiologist	LOM	NIDR
	Graykowski, Edward A.	Medical Director	LOM	NIDR
	Chused, Thomas M.	Senior Staff Fellow	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Recurrent aphthous ulcers, Behcet's disease and Sjögren's Syndrome are three disease states of unknown etiology with oral manifestations. Despite the frequency and severity of these disorders, very few attempts have been made to isolate viruses from patients with these diseases. The basic purpose of this study consists of the diagnosis and attempts to elicit chronic, slow or latent viruses from these patients. This approach will include attempts to demonstrate new antigens or antibodies in these patients.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	32400
TOTAL MAN YEARS:	1.10
PROFESSIONAL:	.60
OTHER:	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John J. Hooks	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-096

Z01-DE-00096-02 CIR C

TITLE OF PROJECT

Diagnosis and Treatment of Dento-Microbic Plaque Diseases

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Keyes, P.H.	Dental Director	CD CI	NIDR
COPI:	None			
OTHER:	Robrish, Stanley A.	Research Microbiologist	CD PR	NIDR
	Wright, William E.	Sr. Dent. Surg. Chief of CDS	CD CI	NIDR
	Webber, Richard L.	Sr. Dent. Surg. Chief of CIR	CD CI	NIDR
	Graykowski, Edward A.	Dental Director	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services
Section: Clinical Investigations
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are to improve the methods used to diagnose and to treat microbic plaque infections that destroy teeth and their supporting structures. Plaques from patients that have dental caries and destructive periodontitis are studied to determine the prevalence of Streptococcus mutans, various actinomyces, and motile forms. The prevalence of these populations and the appearance of lesions are followed as patients follow various experimental programs of dietary, mechanical and chemical therapy directed towards elimination and control of the potentially odontopathic microorganisms mentioned above. New and innovative cultural and microscopic methods are used to detect the presence of the microbes under consideration. Antibacterial agents and fluoride compounds are administered as adjuvants to conventional oral hygiene procedures and regulation of eating patterns.

NIDR CLASSIFICATION: 10400
TOTAL MAN YEARS: 1.00
PROFESSIONAL: 1.00
OTHER:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Paul H. Keyes / R. L. Webber	4/17/7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: NIDR-74A-097

Z01-DE 00097-02 CPR A

TITLE OF PROJECT

Blocking in Dental Clinical Trials

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Korts, David C.	Statistician - Health	CP PR	NIDR
OTHER:	Senning, Rickley S.	Statistician - Health	CP PR	NIDR
	Brunelle, Janet Ann	Statistician - Health	CP PR	NIDR
	Reynolds, George R., Jr.	Statistician	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: NIDR,NIH,Bethesda, MD 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study is designed to determine whether the statistical technique of blocking on baseline DMFS should be used in the design and analysis of dental clinical trials, and to provide specific recommendation for its implementation if it is judged desirable. In addition to treating baseline DMFS as a blocking factor, baseline DMFS is studied as both a single covariate, and also as separate covariates for each group. The problem of lack of balance in blocks and/or groups will be studied.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10500
TOTAL MAN YEARS: .8
PROFESSIONAL: .5
OTHER: .3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David C Korts	4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotioted Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: NIDR-74A-098

Z01 DE 00098-02 CPR A

TITLE OF PROJECT

Evaluation of Three Formulas for Estimating Mean DMFT from Percent of Individuals With One or More DMF Teeth.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	David C. Korts	Statistician-Health	CP PR	NIDR
COPI:	Sven Poulsen	Guest Worker	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: NIDR, NIH, Bethesda, MD 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In 1944 Knutson described a formula for estimating age specific DMFT means from the percent of individuals in the age group having one or more decayed, missing or filled teeth. This formula, together with two other formulas are evaluated simultaneously for different age ranges, and for different allowable maximum percentages. Results indicate that appropriate restrictions of age range, and maximum percent of individuals with one or more DMF teeth, are far more important than choosing the "right" formula. The formula:

$$X = \frac{AY}{G-Y}$$ with A = 3.117 and G = 179, where X is the estimated DMFT mean, and Y is the percent of individuals with one or more DMF teeth is, however, considered preferable to the other formulas based on ease of computation.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10140
TOTAL MAN YEARS: .1
PROFESSIONAL: .1
OTHER: .0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David C. Korts	4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74A-101

Z01 DE 00101-02 CPR A

TITLE OF PROJECT

Gnotobiotic animal studies involving oral Streptococci

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Larson, Rachel H.	Research Chemist	CP PR	NIDR
OTHER:	Stiles, Horace McElreath	Microbiologist	CP PR	NIDR
	Bowen, William	Visiting Scientist	CP PR	NIDR
	Thomson, Lynn A. Jr.	Sr. Dental Surgeon	CP PR	NIDR
COOP :	Germfree Unit, Veterinary Resources Branch, NIH			
	University of Connecticut, Health Resources Center			
	School of Dental Medicine, Farmington, Conn. 06032			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This work involves four phases:

a. Testing in gnotobiotic and barrier maintained rats the cariogenicity of several oral microorganisms.

b. Examining the relevance of symbiotic/antagonistic relationships of Streptococcus mutans and Streptococcus sanguis isolated from the same population to the cariogenicity of these organisms.

c. Evaluation of Actinomyces viscosus in the development of periodontal disease.

d. Study of implantation and distribution of the various sera types of Streptococcus mutans in the mouth of gnotobiotic rats when all types are provided in a common inoculum.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS:	.75
PROFESSIONAL:	.25
OTHER:	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Rachel H Larson	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: NIDR-74A-102

Z01 DE 00102-02 CPR A

TITLE OF PROJECT

Generalized Computer Program for Statistical Evaluation of Longitudinal Clinical Trials.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Brunelle, Janet Ann	Statistician - Health	CP PR	NIDR
Other:	Reynolds, George R., Jr.	Statistician	CP PR	NIDR
	Senning, Rickley S.	Statistician - Health	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: NIDR, NIH, Bethesda, MD 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

A major redesign of an existing clinical trials computer program was undertaken. The objective was flexibility. Consequently, an investigator may designate particular dependent variables such as net increment DMFS, initial normal, erupting teeth, on a study as opposed to receiving total standard information which is not all needed or wanted. The PL/I program also allows the statistical output to be shown for many classifications of individuals such as age, sex, race, school, etc., at one time. Maximum efficiency of computer time and minimal input on user's part are the current objectives.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10500
TOTAL MAN YEARS: .7
PROFESSIONAL: .4
OTHER: .3

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00103-02 CPR A

Prev. Ser. No. NIDR-74A-103

TITLE OF PROJECT

Synthesis of 8-Hydroxyquinolines with potential for long-term anticaries activity

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Mirth, Dale B.	Staff Fellow	CP PR	NIDR
OTHER:	Miller, Carol J.	Bio Lab Tech (Microbiology)	CP PR	NIDR
COOP :	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In an effort to develop new antiplaque-anticaries agents, substituted 8-hydroxyquinolines are being prepared which have the potential for binding irreversibly to hydroxyapatite or proteins on the surface of a tooth. These compounds contain acid hydrolyzable bonds to allow for the slow release of the 8-hydroxyquinoline portion of the molecule at the time of acid challenge, which should result in the suppression of bacterial growth and subsequent plaque formation and caries development. Compounds will be evaluated for in vitro antibacterial and antiplaque effects. Promising compounds will be evaluated for their ability to control experimental dental caries in the rat model.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10510
TOTAL MAN YEARS:	.20
PROFESSIONAL:	.20
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Dale B. Mirth	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-108

Z01 DE 00108-02 LMI B

TITLE OF PROJECT

Immunogenicity of Long-Term Tissue Cultured Mouse Epithelial Explants

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Radentz, William — Guest Worker — LMI NIDR
OTHER: None
COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Epithelial cells of the attached gingiva of mice are being isolated and cultured. The effect of various exogenous and endogenous toxins on these culture cells will be evaluated for their possible role in periodontal disease.

Experiments are in progress to determine the antigenicity of epithelial explants in syngeneic and allogeneic mice. The graft rejection phenomenae will be evaluated for explants which have been maintained in tissue culture for varying time periods.

SPECIAL DESCRIPTORS: 0
NIDR CLASSIFICATION: 20314
TOTAL MAN YEARS: 0.75
PROFESSIONAL: 0.75
OTHER: 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Dr William Radentz per TE	4/23/73

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-109

Z01 DE 00109-02 CPR C

TITLE OF PROJECT

Screening of Dental Patients for the Presence of Streptococcus Mutans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Robrish, Stanley A.	Research Microbiologist	CP PR	NIDR
OTHER:	Keyes, Paul H.	Dental Director	CD CI	NIDR
	Thomson, Lynn A., Jr.	Sr. Dental Surgeon	CP PR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The project involves an estimation of the numbers and Bratthall serologic types of Streptococcus mutans obtained from a variety of the patients seen in the dental clinic. The presence of S. mutans and S. mutans serotypes are to be related to the clinical manifestations of caries in these patients. From this information we hope to gain further insight about the specificity of this suspected odontopath. Other data available from patient records, such as demographic information, manifestations of other diseases, and the presence or absence of specific medication or therapy will be used to develop a better understanding of the ecology of the organism. The systematics of the natural isolates identified as S. mutans will be studied intensively in an attempt to determine the significance of the Bratthall classification and its clinical implications.

SPECIAL DESCRIPTORS: Clinical Trials, Human
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS: .55
PROFESSIONAL: .20
OTHER: .35

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00110-02 LOM B

Prev. Ser. No. NIDR - 74B-110

TITLE OF PROJECT

Detection of Viral Antigens and Antiviral Antibody in Herpes Simplex Viral Infections

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Rosenthal, Joel D.	Biologist	LOM	NIDR
COPI:	Hayashi, Kozaburo	Visiting Associate	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Viral antigens and antiviral antibody can be rapidly detected and quantitated using rapid and simple micro-radioimmunoassays. The binding of radiolabeled antiviral antibody or anti-bamma globulin to fixed viral antigens are used in the direct, indirect, and inhibition tests.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 31300
TOTAL MAN YEARS: 3.10
PROFESSIONAL: .60
OTHER: 2.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Joel [illegible]	4/24/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-111 Z01 DE 00111-02 LOM B

TITLE OF PROJECT

Virus-induced Diabetes Mellitus

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Ross, Michael E.	Research Associate	LOM	NIDR
COPI:	Onodera, Takashi	Visiting Fellow	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of LOM	LOM	NIDR
OTHER:	Brown, Tecolia	Biological Laboratory Technician	LOM	NIDR
	Wheeler, Charles J.	Biologist	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of our work have been to study different facets of animal models of diabetes mellitus. Goals include: 1) the determination of the genetics of host factors that determine the outcome of infection with encephalomyocarditis virus, and 2) the analysis of specific viral factors that cause beta cell infection.

SPECIAL DESCRIPTORS:	Diabetes
NIDR CLASSIFICATION:	34300
TOTAL MAN YEARS:	4.50
PROFESSIONAL:	2.00
OTHER:	2.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Michael E. Ross MD	April 24, 1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-112

Z01 DE 00112-02 CPR C

TITLE OF PROJECT

Screening of Anticaries Agents

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Shern, Roald J.	Dental Director	CP PR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project is to identify agents suitable for short term clinical trials. The materials screened belong to two general categories, cationic antiseptics and antibiotics. Screening is conducted both in vitro and in animals. The in vitro phase screens on such parameters as adsorption, minimal inhibitory concentration, contact angle and modification of enamel dissolution rate. The animal phase measures caries control and plaque control and also monitors untoward effects such as acute toxicity and staining.

SPECIAL DESCRIPTORS:	Human, Clinical Trials
NIDR CLASSIFICATION:	10510
TOTAL MAN YEARS:	.3
PROFESSIONAL:	.3
OTHER:	.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Roald J. Shern	4-21-7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-113

Z01 DE 00113-02 CPR C

TITLE OF PROJECT

Short-term clinical trials of antiplaque agents

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.:	Shern, Roald J.	Dental Director	CP PR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) to identify, adapt and pretest in the laboratory, measurements of response variables including plaque bacteria speciation, cytologic changes and pH modification; (2) to conduct short-term clinical studies of agents which might be capable of restricting plaque and caries. These studies would measure various safety and efficacy parameters of antiplaque agents.

SPECIAL DESCRIPTORS:	Human, Clinical Trials
NIDR CLASSIFICATION:	10520
TOTAL MAN YEARS:	0.3
PROFESSIONAL:	0.3
OTHER:	.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Roald J. Shern	4-21-75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-114

Z01 DE 00114-02 LMI B

TITLE OF PROJECT

Control Mechanisms of IgE Production

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Siraganian, Reuben P.	Medical Officer Research	LMI	NIDR
COPI:	Drobis, Jeffery	Clinical Associate	LMI	NIDR
OTHER:	Fischler, Cynthia	Medical Technician Micro.	LMI	NIDR
	Levin, David P.	Biological Lab. Tech.	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Microbiology and Immunology
Section: Clinical Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The mechanisms that control IgE antibody production are under study utilizing a model syst in mice. Current emphasis is on the measurement of specific IgE produced on challenge by antigen. An assay for quantitating total IgE production is under development. Studies are under way to determine the genetic control mechanisms that determine the amount of IgE produced. Using in vivo cell reconstitution experiments we are studying the defect involved in a strain of mice that is deficient in IgE production.

SPECIAL DESCRIPTIORS:

NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS:	1.90
PROFESSIONAL:	0.90
OTHER:	1.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: NIDR-74A-115

Z01 DE 00115-02 CPR A

TITLE OF PROJECT

The effect of Actinobolin alone and in combination with fluoride on caries experience in rats

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. : Stiles, Horace McElreath Microbiologist
OTHER : None
COOP : None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Actinobolin is an experimental drug (IND applied for) developed originally as a potential anti-tumor agent. It appears to have an inhibitory effect of Streptococcus mutans and has been claimed to prevent the development of caries in rats. This study is attempting to reproduce the results of unconfirmed studies and to investigate additive effect of fluoride at varying levels.

SPECIAL DESCRIPTORS:	None	
NIDR CLASSIFICATION:	10510	
TOTAL MAN YEARS:	.25	
PROFESSIONAL:	.13	Stiles .13
OTHER:	.12	Roseman .12

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00116-02 CPR A

Prev. Ser. No.: NIDR-74-A-116

TITLE OF PROJECT

Effect of Cyancobalamin in caries development in the rat

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Stiles, Horace McElreath Microbiologist

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research, NCP
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study examines the effect of cyancobalamin on the implantation and aggregation of "caries-inducing" streptococci in the rat and its effect on caries development.

Special Descriptors: None
NIDR Classification: 10250
TOTAL MAN YEARS: .43
PROFESSIONAL : .13
OTHER : .30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		3/12/74

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH-1946 (FORMERLY PHS-166)
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: NIDR-74A-117

Z01 DE 00117-02 CPR A

TITLE OF PROJECT

The effect of fluoride on the incorporation and recovery of Ca^{45} from rat's teeth

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Stiles, H. M. Microbiologist
Other: Barry, S.C.
Coop: University of Maryland Dental School

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section : Etiology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Teeth formed in the presence and absence of fluoride are being examined for the release of Ca^{45} when incubated with a cariogenic streptococcus.

Special Descriptors: None
NIDR Classification: 10250
Total Man Years: .5
Prof. : .13
Other : .37

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		5/13/72

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH-1946 (FORMERLY PHS-166)
REV. 6-72

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-118

Z01 DE 00118-02 CIR C

TITLE OF PROJECT

Relationship of the Use of Antiseptics Prior to Oral Surgery and Bacteremia

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sweet, James B.	Sr. Dental Surgeon	CD CIR	NIDR
OTHER:	Brenner, V. J.	Assistant Chief, CP	CP	CC
	Keyes, Paul H.	Dental Director	CD CIR	NIDR
	Robrish, Stanley A.	Research Microbiologist	CD CIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Bacteremias are studied after various presurgical procedures are performed with various antiseptic solutions and again after oral surgery operations are performed within the oral cavity. The data will be evaluated for the variation in the distribution of bacteremias both as a factor of time and which presurgical procedure was performed. The predominant organisms will also be examined.

SPECIAL DESCRIPTORS: Human, Blood
NIDR CLASSIFICATION: 20313
TOTAL MAN YEARS: 1.00
PROFESSIONAL: 0.75
OTHER: 0.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		April 18, 1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-119

Z01 DE 00119-02 CIR C

TITLE OF PROJECT

Effect of Lavage Volumes in Third Molar Surgery

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Sweet, James B.	Sr. Dental Surgeon	CD CIR	NIDR
OTHER:	Abroff, David A.	Dental Surgeon	CD CIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Individuals from ages 15-30 years with bilateral, third molar impactions, indicated for extraction are examined postoperatively for infection and/or localized osteitis. Impacted teeth are removed and the alveolus is immediately irrigated with either high or low volumes of normal saline solution. Five day postoperative healing results are also being examined.

SPECIAL DESCRIPTORS: Human, Blood
NIDR CLASSIFICATION: 20320
TOTAL MAN YEARS: 1.0
PROFESSIONAL: 0.5
OTHER: 0.5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		April 18, 1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00122-02 CPR A

Prev. Ser. No. NIDR-74A-122

TITLE OF PROJECT

Development of Bacteriologic Methods for field studies investigating the etiology of human dental caries.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Thomson, L. Ariel	Senior Dental Surgeon	CP PR	NIDR
COPI :	Little, Wayne	Microbiologist	CP PR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) to develop improved or optimal human dental plaque dispersion methods using sonication techniques, different gaseous environments, or the addition of chemical-enzymatic additives to the dispersion solution; (2) to assess the role of colony crowding on agar plates upon colony morphology and the selective inhibition of certain streptococci on frequently used agar plates; (3) to evaluate selective broths as rapid presumptive tests for the presence of S. mutans in plaque samples.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	10250
TOTAL MAN YEARS:	.75
PROFESSIONAL:	.75
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	L. Ariel Thomson	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR - 74B-123 Z01 DE 00123-02 LOM B

TITLE OF PROJECT

Latent Infection of Sensory Ganglia with Herpes Simplex Virus

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Walz, M. Antoinette	Staff Fellow	LOM	NIDR
COPI:	Asher, L. V.	Visiting Fellow	LOM	NIDR
COPI:	Yamamoto, Hiroshi	Visiting Associate	LOM	NIDR
COPI:	Notkins, Abner Louis	Medical Director, Chief of	LOM	NIDR
OTHER:	Wohlenberg, Charles R.	Biologist	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are the following: 1) to establish a laboratory model of latent herpes simplex infection of sensory ganglia following inoculation by different routes; 2) to study the latency in sacral sensory ganglia following vagino-cervical infection with herpes simplex virus types 1 and 2; 3) to determine, using this laboratory model, the factors involved in viral reactivation; 4) to study the effects of immunization upon the acquisition of ganglionic infection; 5) to develop methods of quantifying the number of cells latently infected and 6) to look for biological or immunological markers of latent infection.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 31300
TOTAL MAN YEARS: 5.70
PROFESSIONAL: 3.20
OTHER: 2.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	M. Antoinette Walz	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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National Institute of Dental Research

Prepared for the Science Information Exchange.

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74B-124

Z01 DE 00124-02 LMI B

TITLE OF PROJECT

Oral Reflexes of the Infant

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Weiffenbach, James M. Research Psychologist CD CI NIDR
COPI: NONE
OTHER: NONE
COOP: Department of Pediatrics, National Naval Medical Center, Bethesda, Md.

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Invest. & Research Services
Section: Oral Pharyngeal Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The discrete elicited lateral tongue movement of the human newborn that was initially described under this project continues to be employed for psychophysical studies of neonatal taste.

The elicitation of tongue movements by individual 5 microliter drops of fluid placed on the tongue is initially independent of taste. However, repeated stimulation with a single fluid leads to decreased response. The adaptation is selective and provides a technique for measuring the tongue's sensitivity to taste. In earlier studies, increments in responding were elicited by adding glucose to the test solution after criterion adaptation to water. This paradigm has now been employed to test the sensitivity of the newborn's tongue to salt solutions.

Since infants have been found to be sensitive to taste at birth it is possible, as has been contended on the basis of animal studies, that early taste experience shapes later food preferences and dietary habits. The reflex measures of taste reception that have been developed here will permit one to investigate whether and by what mechanisms early taste experience prejudices the subsequent development of appropriate eating patterns in humans.

SPECIAL DESCRIPTORS: Human, Psychology, Infants, Biological Science
NIDR CLASSIFICATION: 41323, 105BO
TOTAL MAN YEARS .75
PROFESSIONAL: .50
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	James M. Weiffenbach	4/24/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-127

Z01 DE 00127-02 CIR C

TITLE OF PROJECT

Differences in Immunologic Parameters of Human Subjects in Dentulous and Edentulous States

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wright, William E.	Sr. Dental Surgeon Chief of CDSS	CDSS CIR	NIDR
OTHER:	Oppenhein, Joost	Medical Officer -Research-	LMI	NIDR
	Keyes, Paul	Dental Director	CD CIR	NIDR
	Sweet, James	Sr. Dental Surgeon	CD CIR	NIDR
	Baker, John			
COOP:	Litton Biometics, Bethesda, Maryland			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This investigation is designed to evaluate immunologic parameters (lymphocyte transformation, soft tissue T and B lymphocyte infiltration, immunoflourescence, etc.) pre-and post treatment on patients with severe periodontal destruction.

SPECIAL DESCRIPTORS: Human, Clinical Trial
NIDR CLASSIFICATION: 20220
TOTAL MAN YEARS: 2.0
PROFESSIONAL: 1.0
OTHER: 1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William E. Wright	April 18, 1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

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Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NIDR-74C-128

Z01 DE 00128-02 CIR C

TITLE OF PROJECT

The Effect of Occlusal Loading on the Longevity of Acrylic Dental Implants in Rhesus Monkeys

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Folio, John	Dental Director		CDSS CIR	NIDR
OTHER:	Wright, William E.	Sr. Dental Surgeon	Chief of CDSS	CDSS CIR	NIDR
	Webber, Richard L.	Dental Director	Chief of CIR	CIR	NIDR
	Sweet, James B.	Sr. Dental Surgeon		CDSS CIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Clinical Investigations & Research Services Branch
Section: Clinical Dental Services Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This study proposes to evaluate the clinical, radiographic and histopathologic alterations associated with the effect of occlusal loading on acrylic implants in Rhesus monkeys. Pilot study efforts emphasize the development of appropriate material design, surgical and analytical techniques.

SPECIAL DESCRIPTORS: Primate, Implants
NIDR CLASSIFICATION: 50440
TOTAL MAN YEARS: 1.00
PROFESSIONAL: .75
OTHER: .50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John Folio	April 18, 197

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

No previous serial No.

Z01 DE 00129-01 LOM C

TITLE OF PROJECT

Ultrastructural Investigations of Recurrent Aphthae and Related Human Oral Lesions (C)

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

Principal Investigator: Howell O. Archard Dental Director LOM NIDR
Other Investigators: None
Cooperating Units: Departments of Oral Diagnosis and Oral Surgery, School of Dentistry, University of Alabama in Birmingham

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine

Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Recurrent aphthous stomatitis is a clinically distinctive disease entity that has defied identification of an etiologic agent. Few studies have included electron microscopic analysis and none of an exhaustive nature including three dimensional study have been undertaken. Routine electron microscopy methods are employed on freshly-excised early typical lesions. The lesions are investigated for cytologic changes and evaluated especially for microbial and viral content.

SPECIAL DESCRIPTORS: Human
NIDR CLASSIFICATION: 32300
TOTAL MAN YEARS: .75
PROFESSIONAL: .75
OTHER: .00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	H. O. Archard	

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

Z01 DE 00130-01 LDBA A

TITLE OF PROJECT

Isolation and Purification of Collagen mRNA

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Benveniste, Kathy	Senior Staff Fellow	LDBA	NIDR
OTHER:	Zeichner, Margarita	Visiting Fellow	LDBA	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalie
Section: Connective Tissue
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

We are examining the synthesis of collagen mRNA in connective tissues. The RNA is being extracted and purified and then translated in an in vitro protein synthesizing system derived from wheat germ. DNA complementary to the purified mRNA will be synthesized and used to quantitate mRNA in cultured fibroblasts.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	20322
TOTAL MAN YEARS:	2.25
PROFESSIONAL:	1.75
OTHER:	.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Kathy Benveniste	4/22/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Previous Serial No. None

Z01 DE 00131-01 LMI B

TITLE OF PROJECT

Regulatory Role of Thymus-Derived Lymphocytes on the In Vitro Antibody Response.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Farrar, John J.	Senior Staff Fellow	LMI	NIDR
OTHER:	Fuller-Bonar, Janet	Microbiologist	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The mechanism of the regulatory effect of T-cell mediators on the antibody response is currently under investigation. In vitro co-cultivation and immunization procedures have been used to examine the ability of human peripheral leucocytes (HPL) to reconstitute the antibody response of a population of T-cell deficient mouse lymphocytes to the antigen sheep erythrocytes. Regression analysis of HPL dose response experiments suggest that the HPL contribute a single reconstituting cellular function to the T-cell depleted mouse lymphocytes. The "helper cells" in the HPL population have been shown to be non-phagocytic, radio-resistant, and capable of mediating the facilitative effect via a soluble factor. The soluble mediator has been shown to be released by the HPL when the cells are stimulated by either allogeneic lymphocytes or T-cell mitogens. The results therefore suggest that appropriately stimulated human lymphocytes are capable of replacing one of the T-helper cell deficiencies in the mouse lymphocyte population. It has been shown, however, that the HPL-derived lymphokine does not totally replace the requirement for syngeneic mouse T-cells. If the residual T-cells (approximately 3%) in the mouse lymphocyte population are killed by anti-T serum and complement, the antibody response of the remaining B-cells in the presence of the HPL-derived lymphokine is reduced by 90%.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS;	2.00
PROFESSIONAL:	1.0
OTHER:	1 0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	J. J. Farrar Ph.D.	4/23/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00132-01 NAB C

Previous Serial No. None

TITLE OF PROJECT

A Psychophysiological Evaluation of Intravenous Sedation for Ambulatory Oral Surgery

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Gelfman, Stephen S.	Dental Surgeon	NAB	NIDR
COPI:	Gracely, Richard H.	Research Psychologist	NAB	NIDR
	Driscoll, Edward J.	Chief, Anesthesiology Section	NAB	NIDR
	Sweet, James B.	Sr. Dental Surgeon	CSS	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of the project is to test the effectiveness of two intravenous sedation techniques in an effort to approach an ideal psychophysiological environment for both the patient and the dentist. This ideal environment includes: a) patient cooperation; b) total amnesia; c) minimal physiological challenge; d) rapid complete recovery with minimal side effects; and e) no loss of consciousness or protective reflexes. Technique "a" utilizes methohexital and diazepam. Technique "b" utilizes methohexital, diazepam and sublimaze. The investigators wish to develop a combination of the aforementioned drugs which provide aforementioned above ideal environment and the fastest most complete recovery to enable the patient to return to his daily activities as soon as possible as measured by various sensory, psychomotor, cognitive function and memory tests.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	60410
TOTAL MAN YEARS:	1.0
PROFESSIONAL	1.0
OTHER	.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		4/21/71

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Previous Serial No. None

Z01 DE 00133-01 NAB A

TITLE OF PROJECT

Assessment and Measurement of Experimental and Clinical Pain, and an Evaluation of Pain-Control Agents

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Gracely, Richard H.	Research Psychologist	NAB	NIDR
COPI:	Gelfman, Stephen S.	Dental Surgeon	NAB	NIDR
	Dubner, Ronald	Dent Dir, Ch Neurobiol Anesth Br	NAB	NIDR
	Abroff, David A.	Dental Officer	CSS	NIDR
	Morrow, Irene L.	Dental Hygenist	CSS	NIDR
	Sweet, James B.	Sr. Dental Surgeon	CSS	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are 1) to assess psychophysical methods of experimental pain measurement, i.e., magnitude estimation, category sealing, and cross-modality matching. Pain will be experimentally induced by electrocutaneous, electric tooth pulp, and mechanical heat stimulation; 2) to assess clinical pain measures, such as pain questionnaires and sensory matching methods, in a dental setting; 3) to determine the validity of experimental pain models by comparison of experimental and clinical pain responses; and 4) to evaluate known pharmacological and non-pharmacological pain-control agents.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 60440
TOTAL MAN YEARS: 1.0
PROFESSIONAL .75
OTHER .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard H. Gracely	4/14/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00134-01 LB B

TITLE OF PROJECT

Structure and Biosynthesis of Proteoglycans

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: V. C. Hascall Senior Staff Fellow LB-NIDR

OTHER: None

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Protein Chemistry
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project proposes to study the molecular structure, function and biosynthesis of proteoglycans in normal and abnormal connective tissues, primarily cartilage. Topics of present interest are:

1. The physical properties of monomer and aggregated proteoglycan preparations will be determined utilizing chromatographic, centrifugal and viscosimetric methods. Chemical and enzymatic modifications of proteoglycans will be used to study the chemical substructure of the macromolecules.

2. The characteristics of the interactions of proteoglycans with other matrix constituents will be studied. These interactions include the specificity of binding of proteoglycans to hyaluronic acid and small molecular weight proteins in the formation of proteoglycan aggregates and the interactions of proteoglycans with collagen during fibrillogenesis.

3. Radioisotopic precursors will be used to investigate the biosynthesis of the protein core and the polysaccaride portions of proteoglycan molecules. Model systems, such as the Swarm rat chondrosarcoma and chick limb bud chondrocyte cultures, will be studied to determine their usefulness for biosynthetic experiments.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 20230
TOTAL MAN YEARS: 0.25
PROFESSIONAL: 0.25
OTHER: 0.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Vincent C. Hascall	5-2-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

Z01 DE 00135-01 LDBA B

TITLE OF PROJECT

Morphological and Biochemical Events Involved in the Formation of the Face

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Hassell, John R. Senior Staff Fellow LDBA NIDR

OTHER: None

COOP: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalies
Section: Craniofacial Anomalies
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The migration of the neural crest cells from the neural plate to the mandibular and maxillary processes constitutes the initial step in facial development. Excess vitamin A administered during crest cell migration inhibits the migration of these cells into the facial regions, thereby resulting in cleft palate and short snout. Recent experiments have shown that excess vitamin A stimulates the synthesis of a single glycopeptide in rat liver. Studies are currently in progress to determine the effect of excess vitamin A on glycopeptide synthesis in embryos at the time of neural crest cell migration.

Proper secondary palate formation also involves the elevation of shelves from a vertical to horizontal position. Efforts will be made to develop a culture system which permit in vitro shelf elevation. Using this culture system in conjunction with drugs, it will be possible to directly test the importance of various cellular activities to shelf elevation.

The final developmental event involved in secondary palate formation is shelf fusion. Previous work has shown that the epidermal growth factor (EGF) inhibits in vitro shelf adhesion. Studies are currently in progress to determine the effects of EGF on glycopeptide and glycoprotein synthesis in the palatal shelf epithelium.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 42220
TOTAL MAN YEARS: 1.75
PROFESSIONAL: 1.00
OTHER: .75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	John Hassell	4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00136-01 LOM B

TITLE OF PROJECT

The Role of Different Immunological Processes in Viral Spread

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Hooks, John J.	Sr. Staff Fellow	LOM	NIDR
COPI:	Ida, Shiroh	Visiting Fellow	LOM	NIDR
	Burns, William	Research Associate	LOM	NIDR
	Hayashi, Kozaburo	Visiting Scientist	LOM	NIDR
	Notkins, Abner Louis	Medical Director	LOM	NIDR
OTHER:	Geis, Shirley	Microbiologist	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR/NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: 1) to assay the production of lymphokines, particularly interferon, from immunologically stimulated lymphocytes after in vitro incubation with Herpes Simplex Virus (HSV); 2) to determine if HSV-antibody complexes are capable of eliciti this response; 3) to determine the potential role of immunologically induced interferon in localizing HSV infections; 4) to analyze other viruses which spread from cell to cell and tc determine what immunological processes are required to stop the spread of these viruses.

SPECIAL DESCRIPTORS: Biological Science
NIDR CLASSIFICATION: 31300
TOTAL MAN YEARS: 4.20
PROFESSIONAL: 2.20
OTHER: 2.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Previous Serial No. None

Z01 DE 00137-01 LMI B

TITLE OF PROJECT

Mechanism of Activation of B-Lymphocytes by Mitogens.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Kabir, Shahjahan	Visiting Fellow	LMI	NIDR
COPI:	None			
OTHER:	Rosenstreich, David	Medical Officer - Research	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

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Bacterial endotoxins or lipopolysaccharides (LPS) and some polynucleotides (polyinosinate, polyuridylate, etc.) act as mitogens for bone-marrow derived (B) lymphocytes. The present investigation was initiated in order to find out the mechanism of activation of B-lymphocytes by these mitogens.

Preliminary results indicate that there is a difference in the mode of activation between B-lymphocytes and thymus-derived or T-lymphocytes. While a shorter presence of mitogens in culture is required for the maximum stimulation of T-lymphocytes, a prolonged presence is necessary for the activation of B-cells by mitogens. Binding experiments with radiolabelled mitogens ^{14}C-LPS and ^{3}H-polyinosinate (poly I) suggest that lymphocytes bind these mitogens. B-cells appear to bind more mitogens as compared to T-cells. Further investigation on the mechanism of binding is in progress.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS:	1.0
PROFESSIONAL:	1.0
OTHER:	0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Shahjahan Kabir	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

Z01 DE 00138-01 LDBA A

TITLE OF PROJECT

Exogenous and Endogenous Factors Affecting Normal and Abnormal Development of the Oral Facial Region

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	King, C.T.G.	Research Physiologist	LDBA	NIDR
OTHER:	Wilk, Ann L.	Research Chemist	LDBA	NIDR
	Kushner, David	Research Associate	LDBA	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomali
Section: Craniofacial Anomalies
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Differences in metabolism, placental transfer and fetal binding of teratogens are under investigation. Fetal outcome from prolonged gestation by delay of blastocyst implantation (with phenothiazines) and reinitiation of delayed implantation (with estrogens are being studied.

Animal models are being developed to evaluate the normal and abnormal primary palate formation. For this purpose radiation, cyclophosphamide, cadmium are being used. The different pathways, by which these agents induce clefts of the primary palate are under investigation.

Among other objectives is the development of an in vitro system for direct manipulation of rodent embryos across the critical period of primary palate development. This system will be used to investigate the role of cations (zinc, magnesian iron, cadmium and lead) in the formation of primary palate.

Studies of fetal binding of teratogens, especially of the benzhydrilpiperazine are continuing. The most recent results indicate that norchlorcyclizine (Nor.cc) a major, teratogenic, metabolite of chlorcyclizine, alters acid mucopolysaccharide (AMPS) metabolism in palatal shelves of rat embryos just prior to rotation. Furthermore, experiments suggest that Nor.cc altered the degradation rather than the synthesis of AMPS in palatal tissue.

SPECIAL DESCRIPTORS:	Children
NIDR CLASSIFICATION:	42230
TOTAL MAN YEARS:	5.75
PROFESSIONAL:	4.00
OTHER:	1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
		4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00139-01 LMI B

Previous Serial No. None

TITLE OF PROJECT

Activation of Lymphocytes by Fragments of the Third Component of Complement (C3)

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Koopman, William J.	Staff Fellow	LMI	NIDR
COPI:	Sandberg, Ann L.	Research Biologist	LMI	NIDR
OTHER:	Wahl, Sharon, M.	Staff Fellow	LMI	NIDR
	Mergenhagen, Stephan E.	Chief, Lab. of Micro. & Immunol.	LMI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Humoral Immunity
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Investigations in progress deal with the interaction of the complement system with the cellular immune system. Supernatants of lymphocyte cultures which have been stimulated with C3 and its fragments, C3a, C3b, C3c and C3d , are assayed for a lymphocyte derived chemotactic factor. Although lymphocytes possess receptors for C3, C3b and C3d, only C3 and C3b induce this lymphokine. Studies concerning a modulatory role for C3d are currently in progress.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	20315
TOTAL MAN YEARS:	1.9
PROFESSIONAL:	1.9
OTHER:	0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	William J. Koopman MD	4/23/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH
U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00140-01 CPR A

Prev. Ser. No.: None

TITLE OF PROJECT

Demonstration of Effectiveness of Blocking as a Statistical Technique for Unbalanced Data.

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: David C. Korts Statistician - Health CP PR NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Biometry
Location: ~~NIDR, NIH, Bethesda, MD 20014~~

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Hypothetical examples of dental clinical trial data were developed to demonstrat the utility of a statistical technique of blocking on baseline DMFS. In the five trials studied, crude means ranged from one extreme of highly significant caries reduction in the fluoride group for one trial to the opposite extreme of highly significant caries reduction in the control group for another trial. Blocking on baseline DMFS, however, revealed that the trials were essentially identical.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION:
TOTAL MAN YEARS: .2
PROFESSIONAL: .1
OTHER: .1

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David C Korts	4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. NONE

Z01 DE 00141-01 LBS B

TITLE OF PROJECT

Ultrastructural Studies of rat tail Mineralization

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Kuroda, Setsuo	Visiting Fellow	LBS	NIDR
OTHER:	Nylen, Marie U.	Chief, Lab of Bio Structure	LBS	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The processes involved in mineralization of rat tail epiphyseal plate and tendon are studied in normal and lathyritic animals by electron microscopy using tissues prepared by conventional and by cytochemical procedures. Specific purpose of the study is to attain additional information concerning the role of so-called matrix vesicles and collagen in the mineralization process.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 20230
TOTAL MAN YEARS: 1.75
PROFESSIONAL: 1
OTHER: .75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Setsuo Kuroda	4/23/1975

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

Z01 DE 00142-01 CPR B

TITLE OF PROJECT

A cooperative study of the rat caries model in different laboratories

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Larson, Rachel H.	Research Chemist	CP PR	NIDR
OTHER:	Amsbaugh, Suzanne	Biologist	CP PR	NIDR
COOP :	Harvard School of Dental Medicine			
	Medical College of Georgia, College of Dentistry			
	Ohio State University, College of Dentistry			
	University of Alabama, Institute of Dental Research			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this study is to compare the same rat caries model in the various laboratories and to determine the effect of differences in the models normally used by the investigators. This study should lead to better handling of the animal model and provide for even greater confidence in the results.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10140
TOTAL MAN YEARS: .50
PROFESSIONAL: .20
OTHER: .30

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Rachel H. Larson	4/21/75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

Z01 DE 00143-01 CPR B

TITLE OF PROJECT

Half-Mouth Recording of Dental Caries in Rats

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
OTHER:	Reynolds, George R., Jr.	Statistician	CP PR	NIDR
	Senning, Rickley S.	Statistician - Health	CP PR	NIDR
	Brunelle, Janet A.	Statistician - Health	CP PR	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Prev. Methods Dev.; Biometry
Location: NIDR, NIH, Bethesda, MD 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

To study the feasibility of substituting half-mouth measurement of dental caries in the rat for the purpose of reducing the recording time required by present systems. This will also entail updating of computerized system for recording, collecting and summarizing data from various rat studies.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10290
TOTAL MAN YEARS: .3
PROFESSIONAL: .3
OTHER: .0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00144-01 ODIR B

Prev. Ser. No.

TITLE OF PROJECT

Morphological Atlas of Authentic Type Strains of Microbes (b)

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Love, Leslie L.	Biological Laboratory Technician	ODIR	NIDR
COPI:	Krichevsky, Micah I.	Chief, Microbial Systematics Unit	ODIR	NIDR
OTHER:	Gherna, R. L.	American Type Culture Collection		
	Jong, S. C.	American Type Culture Collection		

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Unit: Microbial Systematics Unit
Location: c/o American Type Culture Collection
12301 Parklawn Drive, Rockville, Md. 20852

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Some of the most commonly used parameters for identifying microorganisms are colonial and cell morphology. However, these parameters are difficult to standardize. One method of standardization is to provide photographs of authentic type strains.

A variety of microorganisms are being photographed in color or black and white. Examples of variation in colony shape, cell size and shape, pigmentation etc., are being recorded under carefully controlled conditions.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 12050
TOTAL MAN YEARS : .75
PROFESSIONAL : .75
OTHER :

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Leslie L. Love	5-29-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00145-01 OD B

TITLE OF PROJECT

Chemical Software

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Medlin, Terry P.	Chief, Scientific Appli Unit	OD	NIDR
COPI:	Taylor, Sheila	Computer Programmer	OD	NIDR
	Rosenberg, Jon	Computer Aid	OD	NIDR
OTHER:	Lee, James R.	Computer Operator	OD	NIDR
	Wright, Vincent A.	Computer Aid	OD	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office; Office of the Director
Section: Data Processing Systems and Analysis
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

1. Design of improved file access methods and hashing functions to improve speed of linkage editor.

2. Development of a multivariate software package geared to statistical analysis of genetic data bases.

3. Design and development of an automated data migration system for storage and retrieval of research data.

4. Design and development of software to calculate velocity in enzyme kinetic studies; automatic detection and calculation of slope in such systems.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	10290
TOTAL MAN YEARS:	2.00
PROFESSIONAL	.25
OTHER	1.75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Terry P Medlin	5-16-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

Z01 DE 00146-01 CPR A

TITLE OF PROJECT

Development of an animal model for studying the effect of antiplaque agents

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Miller, Carol J.	Bio Lab Tech (Microbiology)	CP PR	NIDR
OTHER:	Larson, Rachel H.	Research Chemist	CP PR	NIDR
	Shern, Roald J.	Dental Director	CP PR	NIDR
	Mirth, Dale B.	Staff Fellow	CP PR	NIDR
COOP :	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this study is to develop an animal model for screening antiplaque agents. Due to the availability and adaptability, the rat has been chosen as the model. Further development of this model will involve determining the optimal inoculation procedure and minimal length of time needed to obtain scoreable amounts of plaque. Special attention will also be given to establishing definite plaque scoring criteria.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10230
TOTAL MAN YEARS: .20
PROFESSIONAL: .10
OTHER: .10

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Carol J. Miller	7/22/

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

Z01 DE 00147-01 CPR B

TITLE OF PROJECT

Lectins in the study of plaque and caries development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Mirth, Dale B.	Staff Fellow	CP PR	NIDR
OTHER:	Miller, Carol J.	Bio Lab Tech (Microbiology)	CP PR	NIDR
COOP :	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Preventive Methods Development
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Proteins which interact with certain macromolecules and/or cell types are being investigated for their ability to effect oral components believed to be involved in the formation of dental plaque and caries. Specifically, we are investigating the effect of these proteins (lectins) on: (1) salivary proteins, (2) bacteria involved in plaque formation and caries development, (3) hydroxylapatite - saliva interactions, and (4) hydroxylapatite - saliva-bacteria interactions. These studies will provide a better understanding of caries development and may lead to new ways of inhibiting this process.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10220
TOTAL MAN YEARS: 1.40
PROFESSIONAL: .65
OTHER: .75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Dale B. Mirth	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00148-01 LBS B

Prev. Ser. No. NONE

TITLE OF PROJECT

Fate of Exogenous Tracers in Salivary Glands

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Constance Oliver	Staff Fellow	LBS	NIDR
COPI:	Arthur Hand	Senior Dental Surgeon	LBS	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biological Structure
Section: Experimental Morphology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The handling of exogenous materials by the rat parotid gland is under investigation. Tracers of various molecular weights are presented to the luminal surface of the acinar cells by retrograde injection through the duct, or to the basal and lateral surfaces by intravenous or interstitial injections. The uptake of material and its subsequent utilization in stimulated and unstimulated cells is being followed by light and electron microscopy. Attention is focused on the role of the Golgi complex and lysosomes in the disposition of this material, and on its possible incorporation into secretory granules. Additionally, membrane flow is being studied by use of retrograde injections.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 20216
TOTAL MAN YEARS: 1.75
PROFESSIONAL: 1
OTHER: .75

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
National Institute of Dental Research	Constance Oliver	4/23/7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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U. S. Department of
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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

Z01 DE 00149-01 LDBA B

TITLE OF PROJECT

Extracellular Matrix and Cellular Proliferation During Oral Facial Development

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Pratt, Robert M.	Research Chemist	LDBA	NIDR
OTHER:	Leyshon, Webster C.	Biologist	LDBA	NIDR
	Greene, Robert M.	Fellow	LDBA	NIDR
	Greenberg, Judy	Fellow	LDBA	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Developmental Biology & Anomalies
Section: Craniofacial Anomalies
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objectives of this project are: (1) to define the biochemical nature of the factors regulating cellular proliferation and death during palatal development. The importance that growth plays in palatal elevation is being tested. Precocious activation or inhibition of epithelial cell death involving altered DNA, glycoprotein and lysosomal enzyme synthesis is being tested with various agents such as cyclic nucleotides, steroids and growth factors. Isolated palatal epithelium and mesenchyme are being analyzed and cultured. (2) To determine the biochemical basis for interdigital cell death during normal mouse development and abnormal development in the mouse mutant-Hammertoe; (3) to determine the biochemical nature and role that surface glycoproteins play in normal and abnormal cell interactions during secondary palatal adhesion and neural crest cell migration. These studies will be carried out mainly in vitro visualizing the incorporation of labeled precursors into the surface with autoradiography and with biochemical analysis following release of glycopeptides with proteolytic enzymes. (4) To determine the source and function that hyaluronic acid plays in cranial neural crest cell migration and differentiation.

SPECIAL DESCRIPTORS: Biological Sciences
NIDR CLASSIFICATION: 41211
TOTAL MAN YEARS: 3.25
PROFESSIONAL: 3.00
OTHER: .25

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert Pratt	4/22/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

Z01 DE 00150-01 LOM B

TITLE OF PROJECT

Latent Infection of Autonomic ganglia with Herpes Simplex Virus

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: Price, Richard	Research Investigator	LOM	NIDR
COPI:Katz, Barrett	Research Associate	LOM	NIDR
COPI:Notkins, Abner Louis	Medical Director, Chief of	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The objects of this project are the following: 1) to develop a laboratory model of latent infection of autonomic ganglia; 2) to determine, using this model, the factors involved in viral reactivation, and to study the effect of immunization upon the establishment of this latent infection.

SPECIAL DESCRIPTORS:	None
NIDR CLASSIFICATION:	31300
TOTAL MAN YEARS:	4.60
PROFESSIONAL:	2.10
OTHER:	2.50

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard W Price	4/24/73

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT.

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

Prepared for the Science Information Exchange.

Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Previous Serial No. None

Z01 DE 00151-01 NAB B

TITLE OF PROJECT

The Response of Neurons in the Trigeminal Brain Stem Nucleus to Innocuous and Noxious Stimuli

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Price, Donald D.	Senior Staff Fellow	NAB	NIDR
COPI:	Hu, James W.	Visiting Fellow	NAB	NIDR
	Dubner, Ronald	Dent Dir, Ch Neurobiol Anesth Br	NAB	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Microelectrode recordings from trigeminal nuclei of caudalis are performed in anesthetized monkeys. Mechanical and thermal stimuli, both in the noxious and non-noxious range, are applied to the face and oral mucosa and the response properties of single neurons are recorded and stored on magnetic tape. These neurons are also analyzed with respect to whether they project to the thalamus. Data is analyzed with an on-line, real-time computer system.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	60210
TOTAL MAN YEARS	2.0
PROFESSIONAL	1.0
OTHER	1.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Donald D. Price	April 18, 1975

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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Not for publication or publication reference.

U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00152-01 NAB B

Previous Serial No. None

TITLE OF PROJECT

Psychophysical Measurements of First and Second Pain

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Price, Donald D.	Senior Staff Fellow	NAB	NIDR
COPI:	Hu, James W.	Visiting Fellow	NAB	NIDR
	Gracely, Richard H.	Research Psychologist	NAB	NIDR
	Dubner, Ronald	Dent Dir, Ch Neurobiol Anesth Br	NAB	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Neurobiology and Anesthesiology Branch
Section: Neural Mechanisms Section
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

This project is designed to determine how first and second pain, evoked by a brief heat pulse, are influenced by parameters of peripheral stimulation. Brief painful stimuli are presented to the hands and feet of human subjects. These consist of constant waveform heat pulses that raise skin temperatures of one cm^2 area of skin to noxious levels (45-49°C) for 0.7 sec. No tissue damage is produced. Reaction times and pain magnitude estimations (dependant variables) are made in response to these heat pulses. Independant variables include interpulse interval and location of stimulation site. Data are analyzed with the aid of an on-line computer system.

SPECIAL DESCRIPTORS:	NONE
NIDR CLASSIFICATION:	60214
TOTAL MAN YEARS:	1.25
PROFESSIONAL	1.25
OTHER	.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Donald D. Price	April 18, 19

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

Z01 DE 00153-01 CPR B

TITLE OF PROJECT

Investigation of the oral microflora of patients with Sjogren's syndrome

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Robrish, Stanley A.	Research Microbiologist	CP PR	NIDR
COPI :	Ohwaki, Kyoko			
OTHER:	Chused, Thomas M.	Medical Officer (Res)	LMI	NIDR
	Keyes, Paul H.	Dental Director	CD CI	NIDR
	Wolf, Robert O.	Dental Director	LOM	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Sjogren's syndrome is a rhematoid disease in which xerostomia is a common sympton. Although people suffering from this disease frequently have a high caries incidence, there has been no systematic investigation of their oral microflora. We intend to classify the patients by salivary flow rate and to systematically isolate the microflora from these patients with particular emphasis on the stringent anaerobes. We hope to extend this work to a similar analysis of the oral microflora from people suffering from immune deficiencies.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10110
TOTAL MAN YEARS: 1.0
PROFESSIONAL: 0.5
OTHER: 0.5

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stanley A Robrish	4-22-75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH
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NOTICE OF RESEARCH PROJECT

Prepared for the Science Information Exchange.

Not for publication or publication reference.

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No.: None

Z01 DE 00154-01 CPR B

TITLE OF PROJECT

Chemical products and energy requirements of plaque

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I. :	Robrish, Stanley A.	Research Microbiologist	CP PR	NIDR
OTHER:	Bowen, William H.	Visiting Scientist	CP PR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section: Etiology
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The first attempts will be to standardize plaque samples on the basis of dry weight, DNA, and viable count. Further analyses will be made of the metabolic end products of plaque with various carbohydrate substrates. In addition to this, we hope to quantitate the teichoic acid content of plaque samples from animals.

A second phase of this project is an analysis of the total energy requirements of plaque. When humans or animals are fed by stomach tube so that there are no food accumulations in the mouth, substantial amounts of plaque still form. We intend to determine molar growth yields on pure cultures of plaque microorganisms using the carbohydrate moieties found in the salivary glycoproteins as substrates. Analogous experiments will be done using plaque samples from animals.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 10230
TOTAL MAN YEARS: 0.8
PROFESSIONAL: 0.5
OTHER: 0.3

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Stanley A. Robrish	4-22-7

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DAT

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00155-01 LMI B

TITLE OF PROJECT

The Role of Macrophages in the Activation of T-Lymphocytes

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Rosenstreich, David	Medical Officer - Research	LMI	NIDR
OTHER:	Farrar, J. J.	Staff Fellow	LMI	NIDR
	Dougherty, Suanne	Biologist	LMI	NIDR
	Weedon, Lynda	Biologist	LMI	NIDR
COOP:	None			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Laboratory: Microbiology and Immunology
Section: Cellular Immunity
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data.)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The role of macrophages in the activation of T-lymphocytes induced by mitogens is under investigation. T-lymphocytes do not proliferate at all in response to PHA or Con A unless macrophages are present. Macrophages function in two ways in this response. They bind the mitogen to their surface and "present" it to the T-cell or they release a soluble factor, termed lymphocyte activating factor (LAF), which will enable T-cells that have themselves bound mitogen to proliferate.

SPECIAL DESCRIPTORS:	0
NIDR CLASSIFICATION:	20314
TOTAL MAN YEARS:	1.5
PROFESSIONAL:	0.5
OTHER:	1.0

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	David Rosenstreich Ph.D.	4/23/73

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00156-01 CPR A

Prev. Ser. No.:

TITLE OF PROJECT

Use of mutagens to develop a non-cariogenic Streptococcus mutans strain

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

P.I.: Stiles, H. M. Microbiologist
OTHER: None

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Caries Prevention and Research
Section : Etiology
Location : NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Mutagenic agents are being utilized to derive strains of S. mutans and S. sanguis which have lost cariogenic potential. Animal systems are being used to assess this potential.

TOTAL MAN YEARS: .33
PROFESSIONAL : .13
OTHER : .2

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

NIH-1946 (FORMERLY PHS-166)
REV. 6-72

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U. S. Department of
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00157-01 LB B

TITLE OF PROJECT

Biophysical Studies on the Structure of Connective Tissue

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI: D. A. Torchia Biophysicist LB-NIDR

OTHER: J. R. Lyerla Research Chemist LB-NIDR

COOP: NIAMDD
NBS

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Biochemistry
Section: Protein Chemistry
Location: NIDR, NIH, Bethesda, Md. 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

The purpose of this project is to investigate the molecular structure of collagen, elastin and proteoglycans, and to correlate the results obtained with function. The areas of present interest are:

1. Structure of the terminal regions in the collagen trimer. The aromatic regions of proton magnetic resonance spectra are being used to probe the structure and function of the non-helical portions of the molecule.

2. The structure of elastin. Nuclear magnetic resonance is being used to determine the mobility of elastin chains and elucidate the mechanism of elasticity.

3. The structure of proteoglycans. ^{13}C magnetic resonance is being used to measure the molecular mobility of the polysaccharides and protein chains in cartilage to elucate the molecular structure and interactions in the tissue.

SPECIAL DESCRIPTORS: None
NIDR CLASSIFICATION: 20230
TOTAL MAN YEARS: 1.50
PROFESSIONAL: 1.50
OTHER: 0.0

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Dennis A. Torchia	5-2-75

DO NOT WRITE BELOW THIS LINE – FOR OFFICE USE ONLY

SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Z01 DE 00158-01 CDCI A

Prev. Ser. No. None

TITLE OF PROJECT

Cephalometric description of growth processes through the use of medial axis coding

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Webber, Richard L.	Dental Director Chief CIR	CD CI	NIDR
COPI:	Blum, Harry	Physical Scientist (Res.)	LSMM	DCRT
	Nagel, Roger	Computer Systems Analyst	CD CI	NIDR
OTHER:	Folio, John	Dental Director	CD CI	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION Lab/Branch: Clinical Investigations & Reserach Services
Section: Clinical Investigations
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Efforts to describe cephalometric data more efficiently involve abstracting closed curves through the use of a new geometry of form. The essence of this approach involves recoding cephalometric information in a way which capitalizes on the redundancy of biological growth processes. In this way it appears that fewer degrees of freedom will be required to duplicate the shape of a given structure with a fixed level of error.

NIDR CLASSIFICATION: 43400
TOTAL MAN YEARS: .50
PROFESSIONAL: .50
OTHER:

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Richard L. Webber	4/17/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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REV. 5-70

NATIONAL INSTITUTE OF DENTAL RESEARCH

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U. S. Department of
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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

None

Z01 DE 00159-01 LOM C

TITLE OF PROJECT

Amylase Isoenzymes in Chronic Pancreatitis and Pancreatic Carcinoma

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wolf, Robert O.	Dental Director	LOM	NIDR
COPI:	Ross, Michael E.	Research Associate	LOM	NIDR
OTHER:	Taussig, Lynn M.			(1)
	Stillman, Alfred			(1)

COOP: (1) The University of Arizona, Arizona Medical Center, Tucson, AZ 85724

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Determine the activities of serum isoamylases in patients with chronic pancreatitis and pancreatic carcinoma and compare these values to other standard tests of pancreatic function and morphology. If the evaluation of such isoamylases is sensitive and specific then hopefully this test can replace some of the more complicated tests used for the evaluation of these diseases.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	10400
TOTAL MAN YEARS:	.60
PROFESSIONAL:	.60
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert O. Wolf	4/21/75

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

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NATIONAL INSTITUTE OF DENTAL RESEARCH

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NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPAC

Z01 DE 00160-01 LOM B

None

TITLE OF PROJECT

Oral Pharyngeal Lipase

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Wolf, Robert O.	Dental Director	LOM	NIDR
COPI:	None			(1)
OTHER:	Hamosh, Margit			
COOP:	(1) Department of Anatomy, Georgetown University Medical School			

NAME AND ADDRESS OF APPLICANT INSTITUTION

Lab/Branch: Laboratory of Oral Medicine
Location: NIDR, NIH, Bethesda, Maryland 20014

SUMMARY OF PROPOSED WORK – *(200 words or less – Omit Confidential data.)*

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting resear the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

In the rat the secretions of the lingual glands which empty into the furrows of the circumvallate and foliate papillae of the tongue contain considerable quantities of a lipase. A very potent lipase which hydrolyzes triglycerides to mostly deglycerides and free fatty acids at a pH 4.5-5.5 and has been shown to account for most of the stomach lipolytic activity. This study will attempt to identify the same in the human.

SPECIAL DESCRIPTORS:	Human
NIDR CLASSIFICATION:	10260
TOTAL MAN YEARS:	.25
PROFESSIONAL:	.25
OTHER:	.00

PROFESSIONAL SCHOOL *(medical, dental, etc.)* WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Robert O Wolf	4/21/7

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SUPPORTING AGENCY

METHOD OF SUPPORT *(Check one)*

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETIO

PHS-166
REV. 5-70

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PUBLIC HEALTH SERVICE

NOTICE OF RESEARCH PROJECT

PROJECT NO. (DO NOT USE THIS SPACE)

Prev. Ser. No. None

Z01 DE 00161-01 ODIR A

TITLE OF PROJECT

Standardized Methods for Characterizing Widely Differing Microbial Biotypes (a)

GIVE NAMES, DEPARTMENTS, AND OFFICIAL TITLES OF PRINCIPAL INVESTIGATORS OR PROJECT DIRECTORS AND ALL OTHER PROFESSIONAL PERSONNEL ENGAGED ON THE PROJECT.

PI:	Love, Leslie L.	Biological Laboratory Technician	ODIR	NIDR
COPI:	Krichevsky, Micah I.	Chief, Microbial Systematics Unit	ODIR	NIDR

NAME AND ADDRESS OF APPLICANT INSTITUTION

Office: Director of Intramural Research
Unit: Microbial Systematics Unit
Location: c/o American Type Culture Collection
12301 Parklawn Drive, Rockville, Md. 20852

SUMMARY OF PROPOSED WORK – (200 words or less – Omit Confidential data)

In the Science Information Exchange summaries of work in progress are exchanged with government and private agencies supporting research in the bio-sciences and are forwarded to investigators who request such information. Your summary is to be used for these purposes.

Various methods are being explored to allow characterization and subsequent dentification of widely differing microbial biotypes. The aim is to have standard ethods which allow comparison of fundamental properties of microorganisms to find road commonalities. Simplicity of assessment is a second goal.

utritional requirements in defined media, DNA per cell, protein per cell, DNA to rotein ratio, ultraviolet and visible spectra, selected enzyme levels, guanosine - ytosine content, and logically similar tests are being evaluated.

SPECIAL DESCRIPTORS: NONE
NIDR CLASSIFICATION: 10250
TOTAL MAN YEARS : .75
PROFESSIONAL : .75
OTHER

PROFESSIONAL SCHOOL (medical, dental, etc.) WITH WHICH THIS PROJECT SHOULD BE IDENTIFIED	SIGNATURE OF PRINCIPAL INVESTIGATOR	DATE
	Leslie L. Love	5-29-75

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SUPPORTING AGENCY

METHOD OF SUPPORT (Check one)

☐ Agency Staff (Intramural) ☐ Negotiated Contract ☐ Special Project Grant ☐ Research Grant ☐ Other (Specify)

FUNDS OBLIGATED CURRENT F.Y.	NUMBER OF FUTURE YEARS TENTATIVELY ASSURED BEYOND CURRENT FISCAL YEAR	BEGINNING DATE	ESTIMATED COMPLETION DATE

PHS-166
REV. 5-70

PART II

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

NATIONAL CARIES PROGRAM

July 1, 1974 - June 30, 1975

Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

Preface

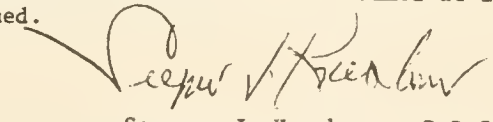
Progress in scientific research is often so subtle that it escapes notice--and the achievements of those individuals who support that research are even less obvious. Only when dramatic discoveries are announced do the contributors to that effort gain some bit of recognition. Still, on a day-to-day basis many dedicated people are working diligently toward that eventual break-through. The annual report at NIH provides each participsnt in the organizational research effort with an opportunity to reflect on, evaluate, and document their contribution to science on an annual basis. This NIDR Annual Report is a record of our Institutes' activities and progress during fiscal year 1975.

For convenience in compilation and distribution, the Report is prepared in five volumes; Part I, Office of the Director and Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Collaborative Research Projects. This is the fourth year that we have combined the individual project report with the SSIE Notice of Research Project form (PHS 166) and find it most effective for our needs. These are printed on blue paper as a separate section of Volume I.

The numbering system has been changed slightly this year to conform with the NIH-wide practice for numbering grants and contracts. All intramural research projects will bear the same number during their life time and will have a "Z01" prefix. The two digits immediately following the five-digit number indicate the number of years that the project, or some identifiable portion of that project, has been active.

It should be pointed out that while the NIDR Annual Report is not a restricted document, it was prepared for administrative use at NIH and not for public distribution. No attempt has been made to evaluate the quality of research--this has been done by study sections, advisory groups or laboratory and branch chiefs--and the comments of the various contributors to this document are their own.

Recipients of this Report are encouraged to familiarize themselves with the Contents and Indexes and constructive criticism aimed at its overall improvement will be welcomed.



Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

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Report of Associate Director

National Caries Program

The National Caries Program is a highly-targeted research and development effort whose mission is the elimination of dental caries as a public health problem in the United States. The general strategy of the Program is to accomplish this mission by identifying and developing agents and technics to prevent the incidence of caries, and to promote their widespread acceptance and use by the public.

A comprehensive Program Strategy Plan has been developed with extensive advice from the dental scientific community, and is implemented through the conduct of direct operations research, research grants and research and development contracts. All three mechanisms are closely integrated and used in complementary fashion to achieve specific program goals.

Program progress and plans are reviewed by frequent workshops and symposia at which expert scientific consultants examine and advise on specific program areas, and by the Dental Caries Program Advisory Committee and the National Advisory Dental Research Council at the regularly scheduled meetings of these standing advisory bodies. During the year, approximately 150 research and development projects were in progress, representing the entire continuum of National Caries Program activity from inquiry into the fundamental etiology of caries, in vitro and animal testing of preventive methods, to clinical trials and community demonstrations.

The laboratories of the Caries Prevention and Research Branch were moved to the Auburn Building and that facility became fully operational, in spite of a continuing shortage of adequate small animal space. A full schedule of experiments on induction of immunization to caries was begun at our newly acquired primate laboratory at Hazelton Laboratories. Over 80 Macaca fascicularus monkeys are now on experimental vaccine regimens.

Significant advances were made in several Program areas. Our extensive field trials of an ultraviolet light-polymerized plastic to seal occlusal surfaces of teeth were completed during FY 1975, and a comprehensive report is ready for publication. The method was shown to provide prolonged protection against caries in children though its cost-effectiveness ratio is less than optimal. Nevertheless, demonstrations of sealant use can now be considered for populations where treatment personnel are readily available.

Four years of research in collaboration with the Center for Disease Control to develop reliable fluorescent antibody technics to identify microflora in dental plaque, resulted in the development of highly specific reagent grade antisera to five of the seven serotypes of Streptococcus mutans. To improve

comparability of data from clinical research we plan to make these conjugates available to grantees and contractors, and contract proposals have been solicited to produce them in the required quantities.

The effectiveness of most caries-preventive agents, including fluoride, could be increased if a method were available to ensure their slow, prolonged and uniform release in the oral cavity after infrequent application. Excellent progress toward this goal was made by two contractors who are attempting to apply existing technology to oral use. One interesting approach involves a combination of adhesive microcapsules with an aerosol delivery vehicle. Clinical trials of one or more of these slow release systems should be possible by the end of fiscal year 1976.

Several pharmaceutical companies submitted candidate oral antimicrobial agents for screening under a program initiated by the NCP in FY 1974. The screening process is long and tedious and is additionally constrained by the great expense of generating the required animal toxicology data before initial human trials are permitted. Nevertheless, two promising compounds reached IND status and will be subjected to FDA Phase I and II clinical study in the Fall of this year.

Perhaps the most significant Program accomplishment during the year was the initiation of a Community Caries Prevention Demonstration Program. In November 1975, nearly 100,000 elementary school children will begin weekly supervised mouthrinsing with sodium fluoride in seventeen selected communities throughout the country. This regimen has been shown to reduce caries incidence up to 40 percent, and is simple and inexpensive. In addition to its promotional aspects, this Community Demonstration Program will permit acquisition of detailed data on the cost and logistics of such programs in a variety of community settings.

This marks the first organized, deliberate attempt to rapidly translate research results on caries prevention into widespread public use, and will demonstrate to the public and profession a thoroughly researched cost-effective (though imperfect) preventive method. That this progress could be achieved in less than four years since the implementation of the National Caries Program is, we believe, directly attributable to the Program structure which permits a high level of day-to-day planning and coordination among direct operations, grant and contract activities.

In the United States there is an acute shortage of "cariologists"; individuals with competence in more than one area of caries research who can successfully coordinate and translate findings from the laboratory to the clinic We have initiated an experimental training program in cariology with multidisciplinary content, and tailored to the background and experience of each trainee. The first such institutional award was made during FY 1975, and four individuals received fellowships for training in previously identified shortage categories.

In the following pages, the major priorities and activities of the National Caries Program during the year are outlined. These are grouped according to the four Program Strategies for Caries Prevention:

STRATEGY I: COMBAT THE MICROBIAL AGENT
STRATEGY II: INCREASE TOOTH RESISTANCE
STRATEGY III: MODIFY THE DIET
STRATEGY IV: IMPROVE DELIVERY AND ACCEPTANCE OF CARIES PREVENTIVE METHODS

STRATEGY I: COMBAT THE MICROBIAL AGENT

Within Strategy Area I are four strategy components (pathophysiology/etiology, epidemiology, antimicrobial and antiplaque agents, and immunization) which are further subdivided into component objectives based upon well-defined program needs. Priority research objectives in this area involve a wide range of approaches concentrated on obtaining the necessary base of information which will allow the Program to design more effective approaches to caries prevention. Some of the priority research needs include: (1) information on the biochemical and genetic virulence characteristics of cariogenic microorganisms; (2) information on salivary and extracellular microbial products contributing to plaque formation and adherence of microorganisms to the tooth surface; (3) information of the etiologic relationships of cariogenic microorganisms in human coronal and root surface caries; (4) development of methods to rapidly identify and quantitate plaque microflora; (5) identification of new agents that will inhibit the growth of, attachment to tooth surfaces of, and/or prevent the release of extracellular products from cariogenic microorganisms; (6) development of standardized procedures for *in vitro*, animal screening, and short and long-term clinical testing of promising anticaries agents; (7) development of methods for prolonged intraoral release of anticaries agents; (8) information on the cell surface of cariogenic microorganisms; the effect of nutrient environments on cell surface properties, mixed cultures (antagonistic relationships), *in vitro* plaque environments (chemostats); (9) information on characterization of antigens from cariogenic microorganisms; (10) information on the effect of salivary immunoglobulins on the implantation of cariogenic microorganisms; (11) information on the selection of antigens as immunogens for a caries vaccine; (12) information on the efficacy of caries vaccine, effective routes of immunization; (13) information on cross reactivity of antigens from oral microorganisms with mammalian tissues; and (14) information on salivary immunoglobulins from populations with different caries experience. The following describes selected highlights of current approaches to caries prevention in the context of the continuum of research activities--problem definition, developmental and clinical--encompassed under NCP Strategy Area I.

Identification and quantitation of plaque microflora

Current interest in the etiologic role of *S. mutans* and other oral microorganisms in human dental caries has emphasized the need for improved technics that will provide accurate recognition and enumeration of those organisms in human plaque samples. Cultivation and quantitative recovery of plaque bacteria presents inherent problems related to the method of plaque sampling and the site selected, oxygen sensitivity of the plaque microorganisms, difficulty of adequate dispersion of bacterial clumps, need for a transport medium in epidemiologic studies, nutritional and selective properties of the medium employed, and the unreliability of identification of bacterial types based upon colonial morphology. Therefore, we have given high priority to research to perfect alternatives to the cultural approach.

Based upon continuing research efforts in NCP laboratories and interagency agreements with the Center for Disease Control, major advances in fluorescent antibody (FA) methodology were made concerning physiochemical characterization of FA reagents, conjugation methods, optimum immunization schedules for S. mutans antiserum and conjugate production, improved specificity of FA reagents for identifying S. mutans by column immunosorption methods. FA staining for S. mutans serogroups in plaque samples appear now to allow application of FA methods to the clinical determination of the etiologic role of S. mutans serogroups in human dental caries. These results were reported at an NCP-supported "Workshop on Fluorescent Antibody and Immunochemical Methodologies Used in the Identification of Cariogenic Bacteria," April 3-4, 1975, in New York City.

Antimicrobial-Antiplaque Agents

Compound screening. The NCP and scientists in the industrial and academic communities share a common desire to identify compounds which can prevent plaque formation, disrupt plaque or render it noncariogenic or enhance enamel resistance. A major problem that has existed for many years in comparing results of tests from different laboratories and clinics stems from the nonstandardized methods and models that are used.

To assist in fulfilling this interest, the NCP has designed a screening program for potential cariostatic agents and has distributed a manual throughout the drug industry which describes uniform criteria for the evaluation of these agents in vitro, in animals, and in clinical studies, and solicits candidate compounds for screening.

Through contracts, and in our own laboratories, about 90 compounds have been screened to date. Of these, approximately 10 merit further clinical testing. The NCP screening program is becoming increasingly popular with pharmaceutical manufacturers as the nature and objectives of the Program become better known. A new contract has been awarded to conduct animal screening of various agents that have been prescreened by industrial submitters for their ability to restrict plaque microorganisms or microbial metabolism. To further develop candidate agents with superior efficacy and safety potential, the NCP has awarded another contract to continue clinical testing using standardized and rigidly controlled protocols. The initial phase of the proposed research involves short-term (i.e., 1-16 weeks) trials in which agent safety, antiplaque, antimicrobial and antimetabolic effects are intensively studied. On this basis, agents are selected for long-term anticaries clinical studies.

NCP direct operations scientists in collaboration with a pharmaceutical company have tested a chlorhexidine analogue, chlorhexidine hydrochloride, in vitro and in animals for antiplaque activity. Another much more promising salt is chlorhexidine hydrofluoride. It has shown high antimicrobial activity in vitro and in animal studies, and appears to be an excellent vehicle for the delivery of topical fluoride.

NCP scientists are also studying derivatives of 8-hydroxyquinolines. It is hypothesized that these chelating agents form a covalent bond with the tooth surface and that the bond is broken by acid hydrolysis, thus releasing the agent. The parent compound, 8-hydroxyquinoline, has shown some toxicity after prolonged use. We are attempting to synthesize derivatives which will be more active and have desirable rates of hydrolysis from the tooth surfaces.

Vehicles for delivery of caries chemotherapeutic agents. The effectiveness of most anticaries chemoprophylactic regimens would be enhanced if the agent were present continuously in the mouth. To achieve this objective, the Program has been looking closely at technics for prolonged slow release or slow activation of agents from small repositories in the mouth. Recently, the NCP initiated two contracts for development and evaluation of oral systems for slow release of fluoride. Devices which give satisfactory slow release in vitro have been developed in both projects and clinical testing is now planned. In another NCP contract, research is being carried out on improving methods for the application of caries-preventive agents utilizing a technic combining microencapsulation with an aerosol delivery system.

Immunization Against Dental Caries

In vitro studies. Grantees have demonstrated that specific antibodies (in secretory immunoglobulin A and also in IgG) can prevent the attachment of S. mutans to smooth surfaces in vitro. Grantees have also shown that the ability of some S. mutans serotypes to adhere to glass surfaces is dependent on the presence of glucosyl transferase and fructosyl transferase on the microbial cell surface, followed by the synthesis of insoluble glucan and fructan from sucrose. The available evidence indicates that the locus of the S. mutans serotype antigen is in close proximity to the enzyme sites on the bacterial cell surface but is not identical to it. Therefore, the antibody may prevent adherence by physically blocking access to the enzyme sites. Studies by several grantees have demonstrated that immunological interference with the activity of S. mutans glucosyl transferase offers the potential to inhibit microbial attachment to the tooth surface.

Animal studies. Results reported by an NCP contractor indicated that rats vaccinated with a glucosyl transferase containing preparation administered through the oral mucosa had less caries than control animals. A grantee immunized rodents with streptoccus-derived dextransucrases administered intraperitoneally and with glycosidic hydrolases injected into the salivary glands with the result that the incidence of caries was reduced. An NCP contractor observed that rats vaccinated in the vicinity of the salivary glands with a preparation of killed S. mutans in Freund's adjuvant, had less caries than controls. Caries reduction was greater on smooth surfaces than on occlusal surfaces.

Results reported in a pilot experiment indicated that Macaca fascicularus vaccinated with a preparation of whole, live S. mutans developed significantly

less caries than the control animals, and their lesions were smaller than those of the controls. These initial studies have been confirmed and extended by NCP grantees and contractors. In studies conducted by an NCP staff scientist, it was reported at a recently convened workshop sponsored by the NCP ("Workshop on the Immunological Aspects of Dental Caries," April 1-2, 1975, New York City), that cell walls derived from S. mutans conferred greater protection given intramucosally than a glucosyl transferase preparation administered through the same route. Using an intraductal route to perfuse washed, formalin-fixed 6715 and crude glucosyl transferase into the parotid ducts of Macaca fascicularus grantees reported at this same workshop an increase of secretory IgA in the parotid saliva of the immunized animals. Additional experiments and assays carried out by these investigators showed that s-IgA in the saliva of these primates was highly specific for S. mutans serotype "d," and markedly inhibited the implantation of S. mutans in the mouth of vaccinated animals. Many of the enzyme preparations have contained additional antigens, antibody to which may have conferred protection. To explore this possibility two contracts have been awarded to study soluble and insoluble antigens from S. mutans.

Human host response to vaccination remains to be studied in detail, effective methods to measure immunoglobulins and antibodies in saliva must be developed, and the effect of various routes of administration using different antigens, as well as the effect of antigens on the biochemistry within plaque must now be determined. NCP contract efforts have been implemented to provide answers to these important problems.

NCP direct operations research on immunization has been sharply expanded. The Program has contracted with Hazelton Laboratories to establish a monkey (M. fascicularus) colony for investigating the effect of selected antigens as appropriate immunogens for a caries vaccine. Various purified and unpurified antigens prepared from S. mutans and other microorganisms which may cross-react with S. mutans, grown under different conditions, and instilled through different routes, are being investigated to determine the optimum method for eliciting a sustained immunologic response and reducing caries incidence.

Although it has now been established in principle that caries can be prevented in animals by immunization, before the method can be considered a practical approach to caries prevention, questions of possible adverse reactions and cross-reactivity of human tissue antigens and microbial cell surface antigens must be exhaustively examined. Grantees are currently studying these phenomena using S. mutans. A contract has also been awarded to screen antigens from selected oral microorganisms for possible cross-reactivity with mammalian tissues. In addition, the NCP will convene a workshop at the NIH in January 1976, to stimulate in-depth discussion and advice to the Program on "Selection of Antigens as Appropriate Immunogens for a Caries Vaccine and Immunologic Cross-reactivity of Antigens from Oral Microorganisms with Mammalian Tissues." Participants will include scientists involved in caries research as well as scientists working with other bacterial vaccines, and on problems relating to cross-reactivity of bacterial antigens with mammalian tissues. Arrangements have been made for participation of individuals from NIAID in this workshop.

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As a mechanism to encourage investigator initiated research on immunologic approaches to caries prevention and related areas under NCP Strategy Area I, a request for grant applications ("Mechanisms for Control of Oral Flora") was published in the NIH Guide for Grants and Contracts Supplement. This announcement evolved from Program analysis of this area which revealed that relatively little research was ongoing, that a considerable portion of this ongoing research would soon terminate, and that this area was ideal for scientific expansion based upon recent findings in primates and other animal model systems regarding the feasibility of the immunological approach to caries prevention and the increasing importance of nonimmunologic host factors as influencing microbial implantation on the tooth surface. Five grants were funded in FY 75 as a results of the response to this announcement.

Microbial Cell Surface of Cariogenic Microorganisms .

High priority is currently given to obtaining better information about surface antigens on the cell wall of oral bacteria. This knowledge is essential to the immunization and the vaccine approach to the prevention of dental caries, for developing better technics of microbial identification and classification, and to understanding the method of attachment of microorganisms to the tooth surface. Cell wall constituents may also be determinants of virulence of cariogenic microorganisms. New grants were awarded to study various in vitro models of the oral plaque environments and plaque formation, including: (1) the interaction of lipoteichoic acids on the bacterial cell surface, lipoteichoic acid binding factors, and anti-lipoteichoic acid antibody in saliva leading to the formation of insoluble aggregates which could, in turn, develop into dental plaque; (2) approaches to interfering with the synthesis and/or incorporation of polysaccharides into the bacterial cell wall via selective transport of inhibitors into bacterial cells; (3) studies on cell wall thickening of cariogenic microorganisms under conditions of nitrogen limitation; and (4) use of the chemostat for studying the effect of changes in growth condition on the surface components and extracellular products, particularly lipoteichoic acid, of cariogenic bacteria singly and in mixed culture experiments. The potential importance of these research efforts is that they involve study of the chemical and biological surface properties of cariogenic bacteria under conditiona aimed at simulating those in the oral cavity. By obtaining a clearer understanding of the effect of environmental conditions on the growth and surface properties of cariogenic bacteria, we expect to obtain a better understanding and appreciation of the factors affecting microbial growth in the oral cavity and their potentia to induce or contribute to the initiation of caries.

Other NCP Initiatives

The NCP believes it is important and timely to critically re-evaluate the status of caries microbiology research, to assess research advances in other areas of microbiology which may be applicable to caries prevention, and to obtain recommendations concerning which problems, projects, and areas of investigation would be the most profitable to pursue in the immediate future in terms of the ultimate preventive goal of the NCP. To that end, the Program has planned a large "Workshop on the Microbial Aspects of Dental Caries" which is to be held in June 1976.

Our epidemiologic studies of root surface caries have suggested that this disease is far more prevalent than previously realized, especially in middle-aged persons.

The NCP published recently a request for grant applications in the NIH Guide for Grants and Contracts Supplement entitled "Root Surface Caries." Specific areas of need which have been identified include approaches to provide a better understanding of the microbial etiology and interactions involved in the initiation and progression of root surface caries as contrasted with coronal caries, the histopathology of this lesion, the destructive potential of the organisms associated with the plaque environment, the methods which could be used to arrest or even prevent these lesions before they become a clinical problem, and the public health, social, and economic significance of the problem itself.

STRATEGY II: INCREASING TOOTH RESISTANCE

The history of public health illustrates that the most effective methods for the improvement of human health are those which prevent the occurrence of disease through increasing host resistance. In the case of dental caries, this approach takes the form of increasing the resistance of teeth to caries attack, and constitutes a major National Caries Program Strategy Area.

Following epidemiologic observations during the early 1900's of the low caries experience of individuals residing in areas with high levels of natural fluoride, the dental research community has developed a fluoride armamentarium which currently includes public water fluoridation, school water fluoridation and various topically applied fluorides. Despite recent progress in other preventive approaches, the use of fluoride remains the most effective and widely used method for preventing dental caries.

Experimental and clinical evidence suggests that the potential of fluoride therapy to prevent and control dental caries is much greater than results currently attained. Further development of these preventive agents is limited by the fact that the mechanism of action of fluoride in the prevention of caries has not yet been completely explained. Both a physiochemical and an antimicrobial activity have been proposed, and evidence exists to support both hypotheses or a combination of the two. The development of an optimum topical fluoride therapy in terms of dosage, vehicle, and treatment regimen would be greatly facilitated by an explanation of the exact mechanisms of action.

To accelerate research on this problem, the National Caries Program has published a request for grant application announcement (RFA) encouraging submission during 1976 of high quality research grant applications proposing investigations which would provide a better understanding of the various mechanisms by which topically applied fluoride exerts its cariostatic effects. In addition, an international symposium on mechanisms of action of fluoride has been planned and will be convened in April, 1976.

Recently reported results from the direct operations research component of the Program indicate that exposure of teeth to low doses of fluoride over a long period of time is far more protective than exposure to higher concentrations for short periods of time, a fact that had not been fully appreciated. These experiments in rodents suggest that topical fluoride therapies could be enhanced by developing methods which provided for a prolonged release of fluoride into the oral cavity. Two contractors have reported progress in this effort. One has developed and is testing in an animal model, an intraoral device to release one milligram of fluoride per day over a six month period. The device is a three layered, fluoride containing, acrylic material weighing about three grams which meters its fluoride release to the rate of salivary flow. Plans are to incorporate this material into a dental restoration or a prosthetic or orthodontic attachment and to conduct human clinical trials of the system in 1976.

The other approach for providing prolonged release of topically applied fluorides involves the microenposulation of fluoride into a delivery vehicle which is strongly adsorped and retained on teeth or oral soft tissues. Success of the principle was reported last year using sodium fluoride encapsulated in methylcellulose. This technique doubled the oral clearance time for fluoride ions over that observed with mouthrinsing techniques. This approach has a great potential for incorporation into cost-effective self-application delivery systems such as toothpaste and mouthrinses, and will be further developed under contract support next year.

Additional possibilities to enhance the efficacy of topical fluorides include modifying the anion portion of fluoride salts. Certain organic fluorides have exhibited increased adsorption activity and some organic antimicrobials form fluoride salts. These properties may maintain or potentiate the caries preventive activities of the fluoride moiety. Salts of polyvalent metals have also shown a potential to enhance fluoride activity. One such compound, titanium tetrafluoride, reduces enamel solubility in vitro more effectively than any currently employed fluoride compound. A three year clinical trial of this agent was initiated in 1975 under a contracted agreement

In spite of the demonstrated potential of fluorides, caries of the biting surfaces of teeth ("pit and fissure" or occlusal caries) remains a serious problem since fluorides provide only one third of the protection to these areas as to the smooth tooth surfaces. Although occlusal surfaces represent only 12.5 percent of all surfaces at risk, epidemiological studies of elementary school children have shown that these surfaces account for as much as 45 percent of the total caries experience. Methods to prevent occlusal caries are, therefore, a matter of our extensive current research interest.

Adhesive tooth sealants to seal occlusal pits and fissures for caries control have been developed over the past seven years by NIDR research grantees. The placement of these materials requires no drilling but rather a slight etching of the enamel surface by short exposure to dilute acid to render it more receptive to bonding. A number of polymers have been tested including cyanoacrylates, polyurethanes and various methacrylates. These are similar in placement characteristics in that the material is flowed into the pits and fissures as a viscous liquid and then polymerizes to produce a clear, hard, uniform resin coating.

A series of pilot studies completed in 1970 resulted in the selection of an ultra-violet light polymerized sealant of the methacrylate type as the best candidate for clinical trials under public health conditions. The National Caries Program initiated five field studies during 1971, using both direct operations and contract support mechanisms, which involved approximately 5000 elementary school children under a wide range of geographic, disease prevalenc and delivery and personnel conditions. These studies were completed during 1975 and the data analyses are nearly completed. As expected, the experience varied among studies in the retention of the sealant material, though in one study, protection of nearly 85% was sustained for over two years. Early concern that the required acid pre-etching of teeth might predispose the tooth

to subsequent caries attack if the sealant were lost, appears unfounded. Another concern that accidental sealing of decayed teeth would result in increased pulpal pathology, was also not substantiated even though carious teeth were purposely sealed in one study. There appears little doubt that adhesive tooth sealants are safe and are effective proportional to their retentiveness. Additional research is planned for 1976 to better define the cost-effectiveness of sealants and to support the development of sealants which will demonstrate high retention even under adverse field conditions.

In addition to the high priority efforts in topical fluorides and adhesive sealants, the Program plans to continue research into the effects of school water fluoridation, combined fluoride therapies and fluoride tablets. These methods are limited in application to specific populations but nevertheless have demonstrated their effectiveness and potential for inclusion into a comprehensive plan for the elimination of dental caries.

The basic structure of enamel and its variation within and between teeth, individuals and populations are being investigated along with the relationship of that structure to variations in solubility and diffusion properties. During 1975 seven research grantees in this area reported new fundamental information on the ultrastructure of enamel which we expect to provide a base from which to understand the preferential nature of the caries process for certain surfaces, and certain routes of dissolution.

STRATEGY III: MODIFY THE DIET

Major Program goals in this Strategy Area involve the identification and development of non-cariogenic dietary sweeteners and dietary additives which will ameliorate the effect of sucrose.

There is irrefutable evidence that dental caries does not develop in the absence of specific dietary substrate and that sucrose is the main dietary culprit. Furthermore, it is known that certain microorganisms (S. mutans) associated with dental caries are particularly adept at forming the adhesive polymers glucan and fructan from sucrose, in addition to having the ability to form acid rapidly. However, the precise role of sucrose in the pathogenesis of dental caries is not completely defined. The formation, composition, and biochemical properties of dental plaque formed in the absence of sucrose have not been studied in a systematic manner, and knowledge in this area might enable us to differentiate plaque which is pathogenic from that which is harmless. To this end, using the contract mechanism, a study was designed to investigate the biochemical composition of plaque in patients who receive their entire diet by gastric intubation. Another group of patients who, because they are fructose intolerant, must avoid all sucrose-containing foods will similarly be studied.

It is frequently stated that the incidence of caries could be reduced by eliminating sucrose from the diet. However, this approach is hardly feasible as a public health measure if only for the reason that most people enjoy eating sweet foods (112 lbs. of sugar per person per year are consumed in the U.S.), and rarely associate their current enjoyment with a future need for dental treatment. Attempts have been made to replace sucrose by simple sugars such as glucose and fructose but, as reported last year, research carried out in our laboratories, and by grantees and contractors, has shown that these sugars are also highly cariogenic. Therefore, we have increased our research effort to identify sweeteners which are non-cariogenic and would be acceptable as a substitute for sucrose. During the year, in vitro and animal experiments by NCP direct operations staff, conducted in collaboration with industry, established that a new sweetening agent, Aspartame, is noncariogenic but does not possess inherent cariostatic properties. However, another substance, xylitol, a pentetol which occurs naturally, is now being actively researched by direct operations scientists. This substance is taste-competitive with sucrose, is noncariogenic and it appears to possess cariostatic properties as well. Plans were finalized to begin a clinical trial of this material in a chewing gum vehicle in FY 1976.

Through the contract mechanism additional compounds are being sought. Research was continued on the sweet protein, Monellin, and two contracts were awarded for study of neohesperidin dihydrochalcones. Both are likely to be noncariogenic and have other industrially desirable properties, and with modification may be suitable sucrose substitutes.

The use of phosphates to overcome the harmful effects of acid production by dental plaque has attracted attention for several years. Results from many laboratories have shown that inorganic phosphates have little cariostatic effect unless they are present in all cariogenic foods, which is clearly impractical. However, a 2-year clinical trial of inclusion of sodium trimetaphosphate in a chewing gum was completed by a contractor in FY 1975 and showed that the phosphate overcame the harmful effects of the sugar in the gum. Short-term clinical studies carried out under contract demonstrated that the organic phosphates calcium glycerophosphate and sodium inositol phosphate have some promise as cariostatic agents because of the biochemical changes they induce in plaque, and the desirability of carrying out full scale anticaries clinical trials is being considered.

Results of a continuing epidemiologic study conducted by direct operating staff in collaboration with the Pan American Health Organization confirmed previous findings that micronutrients other than fluoride may have significant cariostatic properties. Our previous research had demonstrated that high levels of strontium, together with boron, are associated with low prevalence of caries in Northwest Ohio and that, in the Sepik River area of New Guinea, high concentrations of alkaline metals, especially molybdenum, are found where persons have low levels of caries. In the current investigation in Colombia, S.A., persons living in an area where the water contains substantial levels of magnesium, calcium and carbonate have strikingly less caries than those residing in other areas. A comprehensive protocol to study these populations has been completed and the research will continue in FY 1976. Plans were also finalized for a workshop in December 1975, on the role of micronutrients other than fluoride in dental caries. This area must be more actively researched because the observations recorded are illustrative of a naturally occuring public health phenomenon.

The importance of general nutrition in the etiology of dental caries is inadequately understood. During the year a contractor reported that rats which are subjected to protein deficiency have increased susceptibility to dental caries which is associated with altered protein composition of saliva. This observation could, in part, explain why rampant caries often occurs in developing countries following the introduction of sucrose-rich foods.

For many years a group of proteins termed lectins which occur in plants and seeds, have been known to have the property of combining with specific carbohydrate groups. During 1975, NCP direct operations scientists identified a lectin, and are now seeking others, which can interfere with the colonization of the tooth surface by microorganisms. Lectins, because of their property of combining with specific chemical groupings, may also have potential as "homing" agents to deliver therapeutic substances to specific sites.

The investigation of nutritional and dietary influences on dental caries has been hampered by the lack of data which could, with confidence, be compared from one laboratory to another. This problem was in some measure caused

by a lack of conformity in the techniques used in carrying out experiments in animals. In an attempt to obviate these difficulties, a large scale collaborative study was mounted among NCP staff scientists and investigators in four non-Government laboratories. Although the study will not be completed until December 1975, reasons for disparities in results have already been identified, one of which is interpretive differences in the technic of scoring rodent caries. As the study continues, it is certain that other reasons will be identified and the intended end result is the development of an improved rodent-caries model and protocol which will permit direct comparison of data generated in different laboratories.

STRATEGY IV: IMPROVE DELIVERY AND ACCEPTANCE OF CARIES PREVENTIVE METHODS

The possible approaches to caries prevention (e.g., vaccines, bacteriostatic agents, plaque lytic agents, pit and fissure sealants, non-cariogenic foods, etc.) have varying degrees of suitability and value for different U.S. population groups (rural, urban, school children, adult, fluoridated and non-fluoridated areas, etc.) and for different aspects of the disease (pit and fissure, interproximal, smooth surface, and tooth root). Not having the capability to support all feasible approaches, the NCP must allocate its resources carefully among the research and development efforts leading to alternative control measures. This requires some method of predicting the ultimate public health impact of each approach under consideration, and in 1975 we began exploring forecasting techniques to assist in such decisions.

A basic type of information necessary to estimate benefits of preventive techniques is population data on caries experience and on cost of restorative treatment, tooth loss, periodontal disease and other sequelae of caries. In FY 1975 the NCP reviewed data available from the National Center for Health Statistics, the American Dental Association, and from dental health insurers and other groups and commenced discussion with NCHS experts to obtain data more exactly suited to our needs.

A second category of information necessary to estimate benefits is data on level of caries prevention in individuals using a particular control measure (or combination of measures) and data on percentage of individuals using the control measure in "real life" as opposed to clinical situations. As more preventive measures reach the stage of clinical trials, the need for and possibility to undertake cost benefit studies has increased. In FY 1973 we initiated two studies combining all proved technics of caries prevention. First year data on caries reduction in one study now are available. The study conducted in school children with high levels of need for dental care shows an average reduction in caries of approximately 85% in the highly susceptible occlusal surfaces. This intensive prevention program combines optimally fluoridated drinking water, topical treatment of the teeth with fluoride, application of pit and fissure sealants, and oral hygiene education in classrooms.

It may be possible to achieve caries reduction rates nearly this high with a simple combination of topical fluoride treatment and pit and fissure sealants, since clinical trials referred to elsewhere in this report have established that these control measures are selectively effective in controlling caries of smooth tooth surfaces and occlusal surfaces respectively. A study of the cost and benefits when these measures are used together is underway among Navaho school children in New Mexico and a more complex study of these treatments alone and in several combinations was initiated during the year under contract. Unfortunately, the cost of personnel involved in the time-consuming application of sealants (and to a lesser extent, certain topical fluorides) markedly decreases the value of these procedures for large-scale use. Conceivably the cost might be reduced through the use of sub-professionals. To establish

whether high school graduates having no previous dental experience can be trained to apply fluoride and sealants successfully, the NCP with cooperation from the Division of Dentistry has initiated a contract project to develop a curriculum, train an initial group of preventive dentistry aides in these technics, and evaluate their achieved skill. In a second phase of this contract the costs and benefits of a preventive program based on topical fluoride and sealants when applied by the aides will be studied in a closely monitored school-based caries preventive program.

NCP planning is based on making caries prevention simple and inexpensive and, ideally, to require minimum effort from the consumer. Since the greatest caries attack rate is in school-age children, schools conceivably provide an ideal situation in which to deliver these regimens. Nevertheless, the dental professional historically has been regarded as the major provider of such services and oral health messages in the U.S. Since the inception of the program in 1971 we have recognized a need for information on the beliefs of dentists toward the value of preventive dentistry and their current and potential role in the delivery of prevention, and their opinions about the appropriateness of schools and of private dental practice as settings for the delivery of preventive care. Therefore in FY 1974 the NCP implemented through contract with the American Dental Association a major survey among U.S. dentists to answer some of these questions. Eighty-seven percent of the 4000 dentists in the sample responded to this survey. The analysis completed during FY 1975 is interesting and provocative. A few results are: (a) 97% of the dentists agree that there is a great need for a caries prevention program for all school children, (b) 85% indicate that professional societies should assign top or high priority to the promotion of caries prevention for children, (c) dentists would be willing to alter their present practices to participate in an anticaries program, (d) 64% of general practitioners prefer a comprehensive caries prevention program in schools to one in the private practice, (e) 72% of dentists spend less than 15% of their time in the delivery of preventive services to child patients. In summary the survey provides reassurance that the dental profession will significantly assist programs to bring appropriate caries preventive measures to children through schools.

At the beginning of FY 1975 several preventive measures were being tested for safety and effectiveness through clinical trials and one, a weekly mouthrinse with dilute fluoride solution, had passed all tests and been shown inexpensive and simple to deliver as well. The cost of this procedure in school-based programs was estimated to be less than a dollar per child per year and it has been shown to reduce caries incidence between 25 and 40%. It was deemed essential to bring this control measure rapidly into public use. As an alternative to costly and uncertain health education campaigns the NCP decided to test the possibility that this preventive measure (and others with similar potential) could be "seeded" into general use by a national program of community-run demonstrations. These projects would demonstrate the outstanding cost-effectiveness of the measure, provide models that would be convenient and easy for other communities to copy, and provide information on advantages of

school-based caries preventive programs to wide-spread citizen groups. Each community in the program would be kept up-to-date on the level of prevention being achieved and on costs of its project and, in addition, would be required to develop plans to continue the project after a period of federal support. During the year the demonstration program concept was designed and approved and the contract competition widely announced to obtain a variety of project sites. In June sixteen projects were awarded on a nationally distributed basis and with award of a seventeeth contract (to Guam) involve almost 100,000 school children. During the next three years an intensive effort is planned to bring information about these models to the general public and to other community leaders. If this approach has the desired "seeding" effect, other control measures that have successfully passed clinical and cost-benefit trials will be demonstrated for use in appropriate populations.

Delivery of preventive measures under guidance of a classroom teacher involve little effort on the part of the recipient. Others, particularly those designed for use in the home, require that the recipient be motivated to initiate and continue use of them. Consultants have advised that some of our prospective control measures (or some of our attempts to introduce these to communities) may fail because of lack of knowledge of human behavior and motivation. To acquire information on behavioral factors in preventive dentistry the Program is actively encouraging submission of grant applications in this area. In FY 1975 we awarded the first grant to study behavior in use of a caries preventive measure. This research will study the effectiveness of: (1), group discussion and commitment and (2), reenforcement through prizes for children undertaking programs of simple caries prevention. We need much more information on effective communication to instill desire for oral health in children and thus plan to promote this area in the coming years.

Characteristically when carious lesions reveal themselves by pain or discoloration they already need rehabilitative treatment from a dentist. Thus there is little early indication, other than the presence of plaque, that can serve to reenforce personal caries preventive behavior. For several years the NCP has given high priority to developing methods to permit detection of precarious lesions, hopefully at stages where surface damage is reversible. In the public health setting this capability could serve to reenforce patient oral hygiene instruction. In the research area, this capability would be highly valuable for it would allow the conduct of human clinical trials in a greatly decreased time. To develop this capability the Program, commencing in FY 1974, contracted for the development of a system for early detection of smooth surface caries based on penetrating fluorescent dyes. This diagnostic system now is being tested in animal trials. In FY 1975 a second contract was initiated to develop a technic for detecting caries on occlusal surfaces of teeth, using ultrasonic techniques.

PART III

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

EXTRAMURAL PROGRAMS

July 1, 1974 - June 30, 1975

Edited By

Special Assistant for Program Coordination

Extramural Programs

Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

Preface

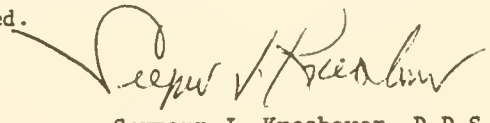
Progress in scientific research is often so subtle that it escapes notice--and the achievements of those individuals who support that research are even less obvious. Only when dramatic discoveries are announced do the contributors to that effort gain some bit of recognition. Still, on a day-to-day basis many dedicated people are working diligently toward that eventual break-through. The annual report at NIH provides each participant in the organizational research effort with an opportunity to reflect on, evaluate, and document their contribution to science on an annual basis. This NIDR Annual Report is a record of our Institutes' activities and progress during fiscal year 1975.

For convenience in compilation and distribution, the Report is prepared in five volumes; Part I, Office of the Director and Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Collaborative Research Projects. This is the fourth year that we have combined the individual project report with the SSIE Notice of Research Project form (PHS 166) and find it most effective for our needs. These are printed on blue paper as a separate section of Volume I.

The numbering system has been changed slightly this year to conform with the NIH-wide practice for numbering grants and contracts. All intramural research projects will bear the same number during their life time and will have a "Z01" prefix. The two digits immediately following the five-digit number indicate the number of years that the project, or some identifiable portion of that project, has been active.

It should be pointed out that while the NIDR Annual Report is not a restricted document, it was prepared for administrative use at NIH and not for public distribution. No attempt has been made to evaluate the quality of research--this has been done by study sections, advisory groups or laboratory and branch chiefs--and the comments of the various contributors to this document are their own.

Recipients of this Report are encouraged to familiarize themselves with the Contents and Indexes and constructive criticism aimed at its overall improvement will be welcomed.



Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

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REPORT OF THE EXTRAMURAL PROGRAMS

NATIONAL INSTITUTE OF DENTAL RESEARCH

July 1, 1974 - June 30, 1975

by

Dr. Clair L. Gardner
Associate Director for Extramural Programs

The Extramural Programs of the National Institute of Dental Research supports research programs ranging from those that deal with basic underlying causes of oral diseases to those that evaluate practical public health measures for disease prevention. These programs include both laboratory and clinical endeavors involving a wide spectrum of scientific disciplines. Accordingly the scientists who administer the NIDR Extramural Programs participate in the planning, development, management, and evaluation of a variety of research and research training projects conducted throughout the United States and abroad. To set the stage for successful achievement of these purposes, the staff makes consistent efforts to stimulate enthusiasm about oral biology research not only among scientists already involved but also among scientists in other fields. These efforts have culminated in an impressive number of basic and clinical scientists from widely different fields directing their expertise toward the ultimate development of preventive measures for oral diseases.

In the two years prior to FY 75, the Extramural Programs of NIDR were marked by internal reorganization and multiple changes in staff assignments. During the past year, however, minimal organizational and personnel changes have allowed the development of a certain stability which has fostered increasing staff efficiency and efficacy. A high level of personal communication among staff and scientists in the field has served to facilitate both administrative and scientific accomplishments.

The only organizational change was the establishment of the new Soft Tissue Stomatology and Nutrition Program by combining the soft tissue diseases component of the old Periodontal and Soft Tissue Diseases Program with the content of the Mineralization, Salivary Secretions and Nutrition Program. This measure gives needed visibility to soft tissue diseases research and is expected to result in expanded activities in this field. New scientist administrators added to the staff during FY 75 were Dr. Paul Parakkal in the Restorative Materials Program and Dr. Vincent Hollis in the Periodontal Disease Program. It should be mentioned as well that Dr. Robert Johnson, of the U.S. Army, completed a highly contributory year in the Pain Control and Behavioral Science Program; and Dr. Carla Evans finished a similarly profitable year working in the Craniofacial Anomalies Program. Towards the end of the year Dr. Robert Schuellein, while retaining his position as Special Assistant for Research Manpower,

transferred his program activities to the newly created Soft Tissue Stomatology and Nutrition Program.

STAFF ACTIVITIES

During FY 75 the three Special Assistants in the Extramural Programs continued their varied activities to facilitate and supplement the contributions of the individual programs. The Special Assistant for Program Coordination again served as editor of the Extramural Programs annual report and as executive secretary of the Periodontal Diseases Advisory Committee. He also organized and chaired the NIDR-AADR forum and developed an exhibit on periodontal disease for display at the NIH Reunion and other scientific meetings. In addition he prepared written material for various Extramural purposes such as budget justifications. As a staff worker in the Periodontal Disease Program he served as a project officer for two ongoing contracts, again authored the program's annual report, contributed to the development of the periodontal disease research evaluation project, and performed other scientist administrator duties as needed. In addition he served as chairman of a scientific symposium at the AADR meeting.

The Special Assistant for Research Manpower prepared an inventory of all manpower studies conducted during the past five years, which was used by Extramural staff to develop a comprehensive analysis upon which to project manpower needs for the next five years. For the National Research Service Awards he participated in the preparation of the guidelines and served as executive secretary for the special ad hoc review committee which evaluated the new Institutional Fellowship applications. In addition he prepared a report for the American Women in Science Civil Action Suit, background material for the Committee on the Needs for Biomedical and Behavioral Research, and information for a Survey of Doctoral Scientists and Engineers. As a staff worker in the Periodontal Diseases Program, he performed a variety of administrative duties.

The Special Assistant for the Dental Research Institutes and Centers (DRIC) again devoted his efforts to management of the DRIC programs and served again as executive secretary of the DRIC Advisory Committee. He also served once more as executive secretary and principal staff resource person on the committee to evaluate the DRIC programs. In addition, he became involved in a variety of special tasks including the development of the meeting on research collaboration by DRIC scientists and NIDR Intramural investigators.

In accord with the annual reports of the last two years Extramural staff have emphasized planning and evaluation of ongoing research more than ever, in spite of the fact that travel funds were somewhat restricted. Informal accountability sessions were continued with program staff to review indepth the progress of each program. Consideration was also given to appropriate program balance. Insofar as individual projects are concerned, staff worked closely with applicants preparing competing continuation grants in an effort to work out realistic long range plans with the appropriate contingencies. Staff made special comprehensive

examinations of all ongoing program projects, so that they could make suggestions to applicants on how they might maximize the productivity of these large group research endeavors, or consider applying for individual project grants. Through earnest discussions of this type during the past several years, staff has been able to reduce the financial commitment of the Institute to program projects, thus providing greater flexibility for future program development.

To assist investigators to better understand NIH support mechanisms, review procedures, and to provide them with essential information on federal funding, staff again conducted discussions throughout the meetings of the American Association of Dental Schools in San Francisco and the American Association for Dental Research (AADR) in New York. At the AADR meeting staff also developed a special forum in which brief presentations were made by staff to inform grantees or potential grantees of areas of emphasis and special programs. In the second part of the forum small group discussions were held concurrently to encourage informal detailed discussion in each of the categorical programs. The forum was well attended and enthusiastically received by AADR members.

COMMITTEES AND SPECIAL PROJECTS

The development of the annual report for the NIDR Extramural Programs was approached in the same fashion as the last two years. The Special Assistant for Program Coordination was again assigned the responsibility for developing a comprehensive series of annual reports which could not only satisfy NIH regulations but could also serve as resource material to aid staff in fulfilling requests for written material throughout the year.

One of the special projects staff became involved in during the year was a review of existing grant and contract management procedures within the National Institute of Dental Research. In this project staff cooperated with Department officials in examining current procedures and developing suggestions for improvements. The report from this project recommended changes in grants management operations with particular reference to post-award administration, budgeting of grant funds and cost analysis. It specifically recommended that NIDR adequately document all post-award monitoring activities. Furthermore, the report suggested that guidelines be set out for reviewing project summaries, conducting site visits, reviewing expenditures and documenting all project modifications. The NIDR is presently developing plans to implement the recommendations set forth. Already extramural staff have completed a new form, described later, which will be used to document staff reviews of annual progress reports.

Another special project is that concerned with the continued refinement of the Operations Manual for Scientist Administrators, a highly useful reference book begun last year. During FY 75 the Manual has been expanded to include an important section on the monitoring of research grant progress reports and plans are under way for developing guidelines to be used by staff in conducting monitoring site visits on ongoing grants. These

changes were recommended as a result of the HEW review of contract and grants management procedures mentioned in the foregoing paragraph. The newly completed progress report form requires specific assessment of research projects, staff comments on problem areas and statements of staff action plus a summary of research highlights. The written results recorded on the new form are expected to serve as a valuable resource to scientist administrators in the management of grants and in the planning of programs. The completed document should also serve as an invaluable aid to other staff in the preparation of written reports for public consumption and for administrative documents, such as the council reports, annual reports, budget narratives, planning documents and Program evaluation reports. Extensive discussions by staff have also resulted in specific plans for expanding the Operations Manual to include a number of other important items. Examples under consideration are: guidelines for critique letters, guidelines for various types of site visits, formats for staff review and processing of various grant applications, guidelines for council presentations, and further development of the formats for the performance of other scientist administrator duties.

The Contract Advisory Review Panel (CARP) established last year to monitor and review Extramural Program's contracts continued and expanded their activity during FY 75. In accord with increasing research contract activity in the Extramural Programs the Committee met four times during the year to review both new and ongoing projects being administered by the categorical programs. Additional information on newly awarded contracts is presented in the funding section of this report.

Last year's annual report referred to a staff committee formed to review the DRG Dental Study Section and suggest possible changes in its mode of operation. The committee recommended that the name of the Dental Study Section be changed; that the scientific expertise in the area of clinical, applied and some basic research be strengthened; and that other DRG study sections which review NIDR proposals include scientists knowledgeable in oral diseases. As a result of the committee's recommendations, the name of the Dental Study Section was officially changed in January 1975 to Oral Biology and Medicine Study Section. The NIDR committee was also requested by DRG to identify scientists from the oral medicine field for potential appointment to study sections which review NIDR applications. The names of 99 scientists were submitted and it is assumed that steps are being taken to make the appropriate appointments.

Previous annual reports have described a special project on the development of an evaluation method for measuring the success of the five university based Dental Research Institutes and Centers (DRIC). In this effort staff and consultants had developed a detailed evaluation outline for comprehensive assessment of the total impact of the DRIC program. However, during FY 75 a critical review by additional consultants and further discussion by staff have considerably narrowed the scope of the project. Meanwhile, the NIDR has initiated a separate series of Institute-wide evaluations of research activities in specific categorical areas. Since

these evaluative efforts will also assess research going on in the DRIC program, the need for a separate study to evaluate the DRIC's seems to be diminished. Consequently, staff will await the findings of the other evaluations before proceeding further with the plans to evaluate the DRIC program.

The first of the Institute-wide evaluations of specific areas covers periodontal research. This project, already launched during FY 75, will comprehensively assess the entire range of periodontal disease research activities supported by NIDR in both intramural and extramural programs. Early in the year, staff of the Periodontal Diseases Program devoted considerable time to the refinement of program objectives to permit more definitive measurement of progress in achieving objectives. These statements were then reviewed by a large number of investigators working in the field and found to be suitable. Subsequently a panel of non-government scientists met to evaluate the 180 research projects considered relevant to periodontal disease. This group will meet again in August 1975 to make judgements concerning the balance of the Institute's programs in this area of research. It is expected that this evaluation project and subsequent efforts in this direction will have a beneficial impact on the future planning of the NIDR's programs.

The purpose of another special project was to conduct a preliminary analysis of the special Dental Research Award Program for young investigators which has been in existence for 5 years. This past year NIDR funded more than 50 of these awards for just over 1/2 million dollars. The recent analysis by Dr. Hayes reports the following conclusions. The program is accomplishing its purpose of providing support to a substantial number of trained investigators. On the average their applications appeared to be of higher quality than regular research grant applications, since they received higher priority scores and higher approval rates. Furthermore, approval rates and priority scores indicated that the special dental research applications are still improving, because the scores of the last three years were higher that the first two. It appears that the process of preparing a special dental research award application is a valuable learning experience for applicants, even if they are not successful. The evidence in favor of this contention is that regular research grant applications submitted subsequent to the submission of a special application enjoyed a higher approval rate and a higher average priority score than regular applications submitted earlier. The analysis indicated that the small dental research grants awards program has been highly successful, not only in providing support to a large number of young investigators, but also in developing meritorious research proposals which have made significant research accomplishments.

WORKSHOPS AND MEETINGS SPONSORED

In addition to their active involvement in many scientific meetings developed by other organizations, NIDR Extramural staff developed six formal workshops, provided funds to support three international conferences, held three

advisory committee meetings, and initiated a unique type of meeting to encourage interaction and collaboration between Dental Research Institutes and Center scientists and other investigators.

Staff of the Craniofacial Anomalies Program organized three of the workshops. One of these important meetings dealt with the psychosocial aspects of craniofacial malformations. This meeting brought together social scientists and dental researchers to systematically examine the entire range of psychosocial impacts involved in craniofacial disfigurement. Consideration was given to such topics as self concept, body image, desire for treatment, and research methodology. It is hoped that this conference will result in beneficial research in this badly needed area. In the workshop on orthognathic surgery, both basic as well as clinical researchers were assembled to reevaluate diagnostic and treatment procedures applied to malformations and to malocclusion. The conference supported by the Craniofacial Program was a week-long meeting on molecular biology in which outstanding scientists from many parts of the world discussed the influence of the extracellular matrix on gene expression. This second international conference was a logical outgrowth of an earlier conference held two years before. The proceedings of this symposium were published by Academic Press in 1975.

Staff of the Periodontal Disease Program conducted three meetings of the Periodontal Diseases Advisory Committee. During the year the Committee spent a major portion of its time discussing the ongoing comprehensive evaluation of the NIDR Periodontal Diseases Research activities. They also discussed the potential value of expanding research on instrumentation, developing clinical cooperative research units, and of conducting technological forecasts for planning purposes. A workshop organized by the Restorative Materials Program brought together scientists working at the forefront of dental implant research. In addition, two international conferences were supported by this program. These included a symposium on the interfacial dynamics of surgical reduction of hard tissues and an annual international symposium on biomaterials.

The Pain Control and Behavioral Studies Program conducted two important workshops during the year. In the first workshop, participating scientists directed their attention to the development of an organized approach to the diagnosis and treatment of pain originating in the oral facial region. The second workshop was the first of a two stage workshop to accelerate research on psychological problems related to dentistry.

The variety of behavioral scientists participating in this workshop concluded that the dental field offered unique opportunities for psychological research and could also benefit greatly from the efforts of research psychologists. The second stage of this workshop project will be held during FY 76.

Finally, in a somewhat unique coordinating endeavor, staff gathered together Dental Research Institutes and Centers scientists, NIDR

Intramural scientists and Extramural staff for a two day meeting to discuss research on Craniofacial Anomalies. The enthusiastic discussion which developed in these fruitful exchanges gave promise for profitable collaborative efforts of many types.

A list of workshops and meetings supported by NIDR Extramural Programs during FY 75 are given below:

STAFF INITIATED WORKSHOPS

1. Psychosocial Aspects of Craniofacial Malformations, Hilton Head Island, South Carolina, October 15-17, 1974.

2. Classification and Nomenclature of Morphologic Defects, Bethesda, Md., February 10-11, 1975.

3. Research Related to Orthognathic Surgery, Bethesda, Md., February 13-14, 1975.

4. Principal Investigators Workshop on NIDR Tooth Implant Programs, New York, N.Y., April 1975.

5. Oral-facial Pain, Bethesda, Md., November, 1974.

6. Psychological Problems Relating to Dentistry, Boulder, Colorado, February, 1975.

NIDR SUPPORTED MEETINGS

1. Second International Santa Catalina Island Colloquium, "Extracellular Matrix Influence on Gene expression," Santa Catalina Island, California, September 19-23, 1974.

2. Symposium on Interfacial Dynamics of Cutting in Dentistry held at the annual meeting of the AAAS, New York, N.Y., January, 1975.

3. Symposium on the Control of Pain presented at the annual meeting of the AAAS, New York, N.Y., January, 1975.

4. Seventh Internationsl Symposium on Biomaterials, Clemson University, Clemson, S.C., April 1975.

Future workshops will include a meeting presently being developed by staff and consultants of the Restorative Materials Program on the interface between biomedical engineering and dental science. This meeting will bring together research engineers and dental scientists to identify areas of dental science which might be significantly advanced by the application of engineering talent. This workshop should logically set the stage

for a workshop on instrumentation to measure periodontal disease being planned by the Periodontal Diseases Program with the aid of the Periodontal Diseases Advisory Committee. The workshop on bioengineering should also be of aid in developing biomedical engineering projects in the craniofacial anomalies area, as was recommended by a workshop in that program. As mentioned earlier, the second stage of a workshop on behavioral science will also be held. In addition, staff of the Dental Research Institutes and Centers and NIDR intramural scientists are expected to develop additional discussions in particular areas of mutual interest. Such meetings will help to avoid unnecessary duplication, enhance collaborative efforts, and should also accelerate research in priority areas.

RESEARCH FUNDING

The NIDR Extramural Programs were able to fund a greater number of new grants during FY 75 than in any previous year. The funding of approximately 100 new grants this past year is in sharp contract with the traumatic experience of funding only 3 new grants during FY 1970. Since that low point there has been a gradual improvement in research funding. A comprehensive picture of research grant funding is given in Table 1, which presents data by program area and by type of grant. This table does not include grants by the National Caries Program, nor the Dental Research Institutes and Centers. As Table 1 indicates, NIDR Extramural provided approximately 14 million dollars to support 265 grants during FY 1975. Of the 265 awards, 193 were made for regular research grants (R01), 14 for program projects (P01), 5 for conference grants (R13), and 53 were special dental grants (R23). Approximately 2/3 of these funds were used to support noncompeting continuation grants, while the remaining funds were used for competing applications. It should be pointed out that the 14 program projects funded during FY 75 consumed only about 20% of the research grant funds, a more favorable proportion than in past years when this figure has approached 40%. It can be seen from Table 1 that the bulk of the funds were employed for the payment of regular research grants. Only small amounts of funds were required to pay the 53 small dental awards. In regard to the distribution of grant funds among programs, Table 1 also shows that two programs, the Periodontal Disease Program and the Craniofacial Anomalies Program, supported approximately 2/3 of the grant projects and used 75% of the research funds during FY 75.

In the Periodontal Disease Program, grant-supported research again emphasized the inflammatory process and host mechanisms of tissue destruction but there was a small shift towards increased efforts in diagnosis, treatment, and prevention. The Craniofacial Anomalies Program invested more than one-third of its funds in cleft palate/cleft lip studies, approximately one-tenth on other congenital anomalies and nearly one-third for studies on malocclusion. Remaining funds were used to support basic studies in developmental biology. The Restorative Materials Program expended the largest portion of its funds for studies on implants, on prostheses and on restorative materials, but also managed to increase its funding

of preventive studies. Program balance was achieved by contracts in certain areas. Staff of the Soft Tissue Stomatology and Nutrition Program were successful in expanding research on nutrition, and in modifying the emphasis of mineralization research so that mineralization studies are now more concerned with biological mechanisms than they were earlier. Finally, the Pain Control and Behavioral Studies Program has achieved a two-fold increase in the number of projects being supported.

To support the five university-based institutes and centers, the NIDR Extramural Program provided 7.4 million dollars. These funds enabled 150 investigators to conduct 180 projects ranging from fundamental problems, such as the role of immunological mechanisms in periodontal disease or the nature of connective tissue destruction to clinical field trials of caries preventing agents and new treatment measures for cleft palate and cleft lip repair. Since the budget for the Institutes and Centers program has been level for the past several years, these programs have been hard hit by inflation. Additional funds would alleviate their present financial crisis.

Advanced planning made it possible to support travel for 75 American scientists participating in the International Association for Dental Research meeting held in London during 1975. To make these funds available and to insure unbiased selection of grantees, a block grant was awarded to the American component of the IADR.

08-04-75
R076

N.I.D.R. EXTRAMURAL RESEARCH GRANTS FUNDED FY 75
DATA AS OF JULY 25,1975
SUMMARY TABLE

CODE/TYPE	PERIODONTAL NO.	PERIODONTAL AMOUNT	CRANIOFACIAL NO.	CRANIOFACIAL AMOUNT	RESTORATIVE NO.	RESTORATIVE AMOUNT	STOMATOLOGY NO.	STOMATOLOGY AMOUNT	PAIN CONTROL NO.	PAIN CONTROL AMOUNT		TOTALS NO.	TOTALS AMOUNT
P01 2	1	$295,562	2	$343,319	0	$0	0	$0	0	$0		3	$638,881
5	3	$777,693	6	$1,333,775	0	$0	2	$333,828	0	$0		11	$2,445,296
AREA TOTALS	4	$1,073,255	8	$1,677,094	0	$0	2	$333,828	0	$0	CODE TOTALS	14	$3,084,177
R01 1	13	$651,092	16	$561,717	20	$950,983	9	$355,628	7	$429,740		65	$2,949,160
2	12	$705,782	15	$951,141	4	$229,791	7	$390,065	2	$127,531		40	$2,404,310
3		$2,610		$48,457		$10,760		$0		$0	***		$61,827
5	29	$1,579,381	25	$1,357,245	15	$691,564	16	$900,721	3	$140,213		88	$4,669,124
AREA TOTALS	54	$2,938,865	56	$2,918,560	39	$1,883,098	32	$1,646,414	12	$697,484	CODE TOTALS	193	$10,084,421
R13 1	1	$35,514	2	$49,330	2	$7,506	0	$0	0	$0		5	$92,350
AREA TOTALS	1	$35,514	2	$49,330	2	$7,506	0	$0	0	$0	CODE TOTALS	5	$92,350
R23 1	8	$87,721	8	$90,444	2	$24,668	5	$57,066	4	$44,057		27	$303,956
5	12	$108,695	6	$52,872	5	$40,080	1	$7,500	2	$20,365		26	$229,512
AREA TOTALS	20	$196,416	14	$143,316	7	$64,748	6	$64,566	6	$64,422	CODE TOTALS	53	$533,468
GRAND TOTALS	79	$4,244,050	80	$4,788,300	48	$1,955,352	40	$2,044,808	18	$761,906	TOTAL EXTRAMURAL	265	$13,794,416

TABLE I

* THIS REPORT DOES NOT INCLUDE NATIONAL CARIES PROGRAM, DENTAL RESEARCH INSTITUTES AND CENTERS OR THE CLINICAL RESEARCH CENTER

** CODES P01 PROGRAM PROJECTS
R01 REGULAR RESEARCH GRANTS
R13 CONFERENCE GRANTS
R23 SPECIAL DENTAL AWARDS

***SUPPLEMENTAL AWARDS

Contract Activities of the Extramural Programs underwent significant expansion in the past year. During FY 75 nine new contract efforts were initiated, bringing contracted research to a total number of 18 projects currently being funded at over a million dollars per year. These projects cover a broad range of scientific endeavor. Two of the new contracts are studies on nutrition in relationship to the integrity of oral epithelium. These projects, developed by staff of the Soft Tissue Stomatology and Nutrition Programs, were funded early in the year. Subsequently staff of this Program participated in the initiation of three contracts to study the therapy of herpes simplex virus infections, a slate of projects undertaken through a special cooperative agreement between the NIDR and the National Institute of Arthritis and Infectious Diseases. In this joint effort, studies will be made of the natural history of herpes infections in humans; and of antiviral chemical agents, such as Ara-A and PAA, which will be tested in double blind treatment experiments utilizing drugs provided by an industrial source. The three new contracts supported by the Periodontal Disease Program include two contracts to support investigations on the Periodontal status of patients with abnormalities of their immune system and one contract to characterize the immune status of patients with severe periodontal disease. The research contract initiated by the Craniofacial Anomalies Program seeks to establish a study of the biological mechanisms of muscle reattachment and migration following osseous surgery. These purposeful research efforts provide needed supplementation to ongoing efforts being supported by grants and thereby furnish a measurable degree of program balance.

TRAINING

The confused atmosphere of research training began to show signs of clearing in FY 75 when the new National Research Services Act became effective. This law reaffirmed federal support for the training of scientists in biomedical and behavioral research. Since the new legislation supersedes the previous training authority, the old training and fellowship programs and the more recent Weinberger postdoctoral programs are being phased out. The new law provided authority to fund both the Institutional Fellowship grants as well as the Individual Fellowship awards.

Table 2 shows the five year distribution of NIDR training and fellowship funds awarded under the three legislative authorities which were simultaneously active during FY 75. The two upper bands show the pattern of phase out being implemented for the old training activities. It may be noted that postdoctoral and special fellowship phase out is being completed during FY 1975, whereas the old training grants will continue to some extent throughout FY 1977. As the upper band shows, a substantial number of trainees are still being supported during FY 75 under funds provided for the 47 ongoing training grants. The fourth band shows that Career Development Awards, after being in serious jeopardy, continued to survive with 25 of these awardees being funded in FY 75. It should be brought out that these awards are now paid from research funds rather than from training funds, and are included here to present a complete

picture of training activities. The three year tenure of the Weinberger postdoctoral fellowship program is depicted in the fifth and sixth bands which show that a fair number of postdoctoral fellows have been able to receive research training under this interim measure. Bands six and seven show FY 75 funding of the National Research Service Awards and projections for funding these awards for the next two years. In spite of extremely late announcements and guidelines, the new training program managed to get off to a reasonable start within NIDR, with funds being awarded to support approximately 82 postdoctoral fellows. The total outlay for training activities in NIDR has remained somewhat level during the past five years in spite of the drastic changes that have taken place.

Table 2. FIVE YEAR DISTRIBUTION OF NIDR TRAINING AND FELLOWSHIP FUNDS

Funding Mechanism	FY 73	FY 74	FY 75*	FY 76+	FY 77+
No. Training Grants (OLD)	87	60	47	34	16
No. Trainees	380	298	225	170	80
FUNDS$(000s)	$2,989	$4,189	$2,869	$2,298	$1,264
No. Postdoctoral and Special Fellowships	38	18	3	0	0
FUNDS $(000s)	$507	$219	$47	0	0
No. Career Develop. and Career Awards (OLD)	22	17	25	19	11
FUNDS $(000s)	$506	$406*	$591*	$358*	$272*
No. Institutional Fellowship Grants (Weinberger)	-	15	15	15	-
No. Fellows	-	52	69	71	-
FUNDS $(000s)	-	$883	$1,181	$1,259	-
No. Postdoctoral Fellowships (Weinberger)	-	47	15	21**	-
FUNDS $(000s)	-	$526	$258	$302	-
No. Institutional Training Grants (National Research Service)	-	-	10	15	25
No. Fellows	-	-	42	75	125
FUNDS $(000s)	-	-	$650	$1,400	$2,300
No. Postdoctoral Fellowships (National Research Service)	-	-	40	50	70
FUNDS $(000s)	-	-	$447	$715	$1,010
Total No. Individuals	440	432	419	406	286
Total Funds $(000s)	$4,002	$5,817	$5,452	$5,974	$4,574

* Paid from Research Funds - not included in Totals.
** Eleven postdoctoral fellows chose to activate their grant in FY 75.
\+ Figures in this column are estimates.

RESEARCH HIGHLIGHTS

In the paragraphs to follow, selected research findings made by NIDR-supported investigators are presented in a condensed form. More expanded descriptions are given in the reports of the individual programs. Highlights in periodontal disease research involved pathogenic organisms, virulence mechanisms, endotoxins, immune inflammatory mechanisms, and the efficacy of preventive measures. Studies on pathogenic organisms showed that 5 groups of Gram-negative anaerobic rods were predominant in periodontosis, whereas Gram-negative anaerobic rods of a different type inhabited lesions of rapidly advancing periodontitis. When representative strains of the organisms from both of these conditions were implanted in germ free rats, severe disease with bone loss resulted. Fourteen other suspected pathogens failed to cause disease. In studies on the virulence of Actinomyces viscosus investigators obtained evidence that plasmids, extrachromosomal pieces of DNA, change the bacterium to a virulent form. As a result of being infected by a plasmid, virulent strains make a specific antigen and a mitogenic peptidoglycan and cause periodontal disease in animals. The avirulent strains do not contain plasmids and do not possess these characteristics. In a 4 year study, gingivitis in beagle dogs progressed to periodontal bone loss, but some dogs had gingivitis which did not lead to bone loss. These results suggest that gingivitis may not always progress to bone resorption. Other studies indicated that bacterial endotoxins from dental plaque do not penetrate into the periodontium unless there is damage to the epithelial lining, but endotoxins do become absorbed to tooth surfaces where they prevent the reattachment of healthy cells. If the endotoxin is removed, cells attach freely to these surfaces suggesting that endotoxin removal could make clinical reattachment possible. Since bacterial antigens may gain access to the gingiva and form complexes with antibody, an investigator injected immune complexes into tissues. His finding that they caused alterations in osteoblasts and fibroblasts suggests that these complexes may inhibit new bone and collagen formation. In studies on the regulation of the immune response, investigators found that normal humans have a serum factor which suppresses the chemotactic responsiveness of monocytes. The inhibitory factor was elated in a group of patients with high susceptibility to infection. In another study investigators detected a serum factor which inhibits lymphocyte transformation. Evidence obtained in several studies suggests that cell-mediated immunity may not be involved in periodontal disease. When cell-mediated immunity was inhibited in monkeys, in rice rats and in hamsters either by thymectomy, or by antithymocyte globulins, all of the animals still developed periodontal disease. Furthermore, no correlation between disease severity and signs of cell-mediated immunity were seen in patients with varying degrees of periodontitis, nor in patients developing experimental gingivitis. Studies on collagen synthesis brought out details on the dynamics involved in procollagen formation, while other studies on normal connective tissue emphasized the proteoglycans. In both animal and human specimens, it was shown that the collagen of the periodontal ligament is quite stable and undergoes little turnover. Studies on collagen metabolism in disease have shown how collagen degradation or synthesis may be altered. In one study cells associated with humoral immunity caused lysis of human fibroblasts. Other studies showed that diseased human and marmoset gingiva produce less collagen than healthy gingiva. Scientists have also shown that collagenase exists in human gingiva in a latent form which can be activated directly by bacterial stimulation or indirectly via inflammatory mechanisms. Studies on the Osteoclast Activating Factor (OAF)

indicate that production of OAF by lymphocytes precedes cell transformation, and that B-lymphocytes rather than T-lymphocytes may be the source of OAF. Other investigations showed that prostaglandin accounted for much of the bone resorptive activity in the gingiva of monkeys. Dogs with severe periodontitis showed elevated heparin levels, a finding of interest since heparin enhances both bone resorption and collagenase activity. Research on treatment and prevention indicates that both mechanical therapy and chemotherapy have value. Mechanical and surgical treatment coupled with systemic antibiotics maintained periodontal health in seven patients with periodontosis for 3 years. In a long-term study beagle dogs with unbrushed teeth developed typical periodontal disease, whereas dogs with teeth brushed twice each day showed no findings.

In the area of growth and development electron microscopic studies of gene expression at the cellular level have identified stem cells for pre-odontoblasts in dental papilla mesenchyme derived from neural crest cells. Acridine orange was used as a marker for identifying the "transcriptively-active" areas of chromatin within these cells. Other studies indicated that H-2 histocompatibility antigens are expressed on the surfaces of embryonic mouse cells during tooth formation. A study of bone matrix indicated that bone morphogenetic protein is chemically-bonded to collagen. The significant discovery that triamcinolone acetonide will induce clefts of the secondary palate in monkeys gives researchers a new primate model for oral clefting. Studies of fusion showed that glycoproteins present on the palatal epithelial surfaces may increase adhesiveness prior to epithelial breakdown and fusion. Fusing epithelium was also found to contain only small amounts of glycogen, making the absence of this substance a good histologic marker for cell death. Scanning electron microscopy showed that alterations occur in palatal epithelium even before the shelves contact each other. Human studies in the genetics of cleft lip/palate have shown that certain loci such as the major histocompatibility complex and some lymphocyte-defined loci, may be inherited atypically in cleft palate families. In an analysis of family pedigrees, the data suggested that cleft lip with or without cleft palate and cleft palate are caused by a single genetic system rather than two genetic systems. Oral clefts were found to affect many aspects of daily life. Individuals with clefts marry later and have fewer children than those without clefts and the parents of a child with an oral cleft may be reluctant to take pride in or care for their child. A classification of cyclopia on the basis of accompanying malformations has made it possible to counsel families on the likelihood of having another cyclopic infant. In studies on the interplay between genetic and environmental factors in craniofacial growth, independent genetic influences were detected for mesiodistal and buccolingual tooth dimensions. Gene loci were determined which accounted for much of the variation in tooth size. Maxillary midline diastema were found to occur more often in black children than in white children. Fluorouracil, a cancer chemotherapeutic agent, was found to inhibit the growth of the cranial synchondroses and consequently might adversely affect the craniofacial growth of young individuals. In the field of malocclusion advances were reported on the cellular aspects of tooth movement, on the changes in anatomic structures during orthodontic treatment, and on blood flow after orthognathic surgery. Using new methods for measuring cyclic adenosine 3', 5'-monophosphate (cAMP) in bone and for localizing the nucleotide within the cell investigators found increased cAMP activity around specific areas of erupting and orthodontically moving teeth. In a primate study of the effects of high pull extraoral headgear, it was found that the use of this appliance affected other cranial structures also, including the cranial base, the mandible, and the temporomandibular joint. In experimental studies on

surgical correction of malocclusion, investigators found that selected maxillary osteotomies will significantly expedite movement of the maxillary bones during treatment with expansion appliances.

In restorative materials research, composite resins continue to show improvements, but they are not yet suitable for posterior teeth. In a rigorous clinical evaluation, the performance of amalgams, composite resins, and a silicate were compared over a 3 year period. The study showed that the composites were superior in marginal adaptation, but the amalgam retained its anatomic form better. In the area of tooth implantation, bioglass and titanium wire seem promising. In fact, cylindrical titanium wire implants have been so successful in baboons that it may soon be appropriate to consider clinical investigations on this material. Early studies on maxillofacial prosthetic materials indicate that silphenylenes and terpolymers may prove superior to the silicones and polyvinyls currently used. These new materials score higher in tensile strength, staining characteristics and weatherability.

In a study on nutrition, it was shown that a deficiency of ascorbic acid causes effects at two different levels. At the molecular level, inadequate ascorbic acid results in collagen fibrils deficient in hydroxyproline which appear as denatured chains rather than as the typical triple helix structure. At the cellular level there is a failure of differentiation and drastic changes in the morphology of developing scorbutic tooth germs. In in vitro tests of guinea pig tissues, vitamin C deficiency appeared to cause an increase in oral mucous membrane permeability, a manifestation likely to result in increased susceptibility to local disease. Although it was demonstrated earlier that vitamin D was required for cross-link formation in bone collagen, recent studies indicate that the vitamin is not required for cross-links in skin collagen. In primate studies malnourished animals showed more alveolar bone resorption and more atophy of periodontal fibers than controls. Recent neurophysiological studies on the salivary glands have shown that the parasympathetic branch induces mitotic bursts and an increase in parenchymal cell size in the parotid glands when secretory activity is abruptly increased. The sympathetics appear to be essential for adequate emptying of amylase from the parotid when fasting animals are given solid food. In mineralization studies it was shown that an intracellular nucleating vesicle initiates calcification in the jelly fish statolith and that fossils from the Cambrian period may contain well-preserved collagen. After a 12-year study which showed a declining incidence of recurrent aphthous ulcers (RAU), the authors concluded that a high frequency of RAU occurs during student years because of increased stress during this period. In the area of pain and behavior, progress was made in understanding how acupuncture works in pain relief, and in the etiology and therapy of myofascial pain-dysfunction syndrome (MPD). The study on MPD demonstrated that stress in MPD patients caused increased masseter muscle activity, a finding which suggests that the muscles of mastication are target tissues for stress in these patients.

Prepared by A. A. Rizzo

ANNUAL REPORT FY 75

PERIODONTAL DISEASE PROGRAM

INTRODUCTION

The Periodontal Disease Program fosters research related to the etiology, pathogenesis, diagnosis, treatment and prevention of periodontal diseases. These research activities were formerly administered as part of the Periodontal & Soft Tissue Diseases Program, which was modified in April 1975 by transferring the soft tissue diseases projects to a program now called the Soft Tissue Stomatology and Nutrition Program. Thus, the present Periodontal Disease Program is now devoted entirely to periodontal research, a change in accord with expanding activities in this field. The ultimate mission of the program is to develop new knowledge which will lead to the prevention and eradication of periodontal diseases throughout the world. Since these diseases are multifactorial in etiology and complex in manifestation, the program supports research and training efforts in a wide variety of subject matter. Included are studies on microorganisms, their biology, chemistry, effects on the host, and behavior in the oral environment, as well as studies on the structure and metabolism of the periodontal tissues in health and disease. Within the broad spectrum of biological studies supported, special attention is given to the biochemical and immunologic mechanisms involved in the pathologic processes of inflammation and tissue destruction. It is hoped that comprehensive studies of the chemical steps involved in periodontal disease progression will reveal optimum points at which inhibitory agents can prevent permanent loss of tissue.

During the past year there has been increased emphasis on the immunologic aspects of periodontal disease, as well as new findings on the etiologic microorganisms which appear to be involved in different forms of the human disease. These scientific achievements have come about through continuing collaboration involving American and European investigators of many disciplines working in numerous centers and universities. A description of research highlights from these multidisciplinary endeavors is presented in the text of this report. Also included is a report on the distribution of research and research training funds, an account of staff activities during FY 75 in carrying out their responsibilities as scientist administrators and an outline of future program plans.

ADMINISTRATIVE

During the past year, the program awarded research funds of approximately $4.2 million to support 4 program projects, 54 regular research grants,

1 conference grant and 20 Special Dental Research Awards. Thirteen of the regular grants were new awards and 8 of the Special Dental grants were new applications. Research training awards included eleven training grants, which provided stipends for 41 trainees at a cost of $629,856. The program also awarded $102,043 for 14 postdoctoral fellows, 7 of which were new applications. In addition, one career and 3 career development awards were made at a cost of $98,342. In the area of collaborative research, two new contracts were awarded to provide support for investigation on the periodontal status of patients with abnormalities of their immune system, and one contract was awarded for a study on the immune status of patients with severe periodontal disease. The expenditure for these contracts was $398,535. Renewal of previous contract commitments brought the program effort in this are to $512,162.

Table 1 shows the distribution of research grant funds according to subject area. This past year witnessed a small redistribution of funding from the heavily supported areas of etiology, and tissue destruction to the areas of diagnosis, treatment, and prevention. The increase of effort in the latter areas was a result of staff programming activities.

TABLE I

Periodontal Disease

A. Etiology	
Plaque (microbiology, chemistry, adhesion, toxicity, salivary and dietary factors)	$855,179
Miscellaneous factors	38,326
B. Pathogenesis and Pathology	
Inflammatory response (Chemotactic factors, vascular effects immune response, chemical mediators)	1,183.443
Tissue destruction and healing (epithelial integrity, connective tissue and bone metabolism, effect of inflammation)	1,190,871
Miscellaneous	337,450
C. Diagnosis and Treatment	91,459
D. Prevention	149,745
Subtotal:	3,846,473
E. Soft Tissues* (Herpes, Aphthous ulcers, tumors, pulp)	397,577
Total:	$4,244,050

* To be transferred to other programs.

STAFF ACTIVITIES

During the year, staff made visits to a number of institutions for the purpose of programming, monitoring and evaluating proposals, and also to participate in meetings. Visits were made to ten institutions to discuss program efforts in periodontal disease, and five universities were site visited in connection with grant applications. Staff also made a project site visit to one of the Dental Research Institutes to become familiar with ongoing research. Members of staff were involved in collaborative research efforts as project officers, and therefore, visited two institutions to monitor existing contracts and three others to negotiate new contracts. The latter half of the year found staff very involved in the formal evaluation of all of the Periodontal Disease Research Activities of NIDR. Staff also participated in the following scientific meetings:

1. Periodontal Disease Symposium, Chicago, Illinois, July, 1974.

2. American Academy of Periodontology, Atlanta, Georgia, October, 1974.

3. Oral and Perioral Ulcerations Symposium, Ann Arbor, Michigan, October, 1974

4. American Dental Association, Washington, D.C., November, 1974.

5. American Association for the Advancement of Science, New York, New York, January 25-31, 1975.

6. Extramural Funding Symposium, North Carolina A & T State University, Greensboro, North Carolina, February, 1975.

7. Twenty-eighth Annual Symposium on Fundamental Cancer Research, University of Texas Cancer Center, Houston, Texas, February 26-28, 1975.

8. Symposium on Immunological Aspects of Dental Caries, New York, New York, April 2-3, 1975.

9. American Association for Dental Research, New York, New York, April 4-8, 1975 (Dr. Rizzo was chairperson for a symposium.)

10. American Society for Microbiology, New York, New York, April 27-May 2, 1975 (Formal presentation by Dr. Hollis.)

11. Ninth Miles International Symposium on Cell Membrane Receptors for Viruses, Antigens and Antibodies, Polypeptides, Hormones and Small Molecules, Baltimore, Maryland, June 4-6, 1975.

12. Third International Conference on Periodontal Research, Airlie, Virginia, June 22-27, 1975. (Dr. Rizzo served as editor of discussion summaries,)

The following professional development meetings and courses were attended by members of program staff:

1. Grants Associate Seminar Series, NIH, March-June, 1975, (Dr. Hollis).

2. Overview of Contracts and Grants, Continuing Education Programs, Staff Training, Extramural Programs, NIH, March 10-11, 1975, (Dr. Hollis).

3. Program Planning, Evaluation and Analysis, Continuing Education Programs, Staff Training, Extramural Programs, NIH, May 12-14, 1975 (Dr. Hollis).

4. STEP Module on Committee Management Airlie, Virginia, March 3-5, 1975 (Dr. Rizzo)

RESEARCH HIGHLIGHTS

Periodontal disease research highlights during FY 1975 include additional progress in identifying pathogenic organisms associated with different forms of disease and early evidence that the plasmid theory of virulence may be applicable to some of the newly discovered pathogens. Other pathogenicity studies brought out the possibility that endotoxin may not only play a role within the periodontal soft tissues, but may also impart to the tooth root toxic activity which prevents reattachment of tissues. Evidence was also adduced from several sources that humoral immunity mechanisms may cause a net loss of periodontal collagen and bone by specific adverse effects on fibroblasts and osteoblasts. While studies on treatment have emphasized the use of antibacterial agents in humans and animals, the long term benefits of mechanical hygiene in preventing periodontitis were demonstrated. Brief descriptions of these interesting projects are given in the text to follow.

Etiology

Last year's annual report referred to microbiologic studies at Forsyth Dental Center and Harvard University on the severe form of periodontal disease called periodontosis. Since then, the development of new types of growth media have facilitated additional cultural studies at these institutions on patients with periodontosis and patients with rapidly advancing adult periodontitis. Such studies indicated that a specific group of microorganisms colonize the advancing front of periodontosis lesions, and that a strikingly different group of microorganisms colonize the lesions of rapidly advancing periodontitis in adults.

In periodontosis lesions, five groups of Gram-negative, anaerobic rods predominate. These include: (1) saccharolytic vibrios, (2) surface translocating fusiform rods for which the genus name Capnocytophaga has been proposed, (3) tiny rods 0.3 x 0.8 micron in size, (4) short, round ended, saccharolytic rods, and (5) surface translocating blunt ended, large rods distinct from Capnocytophaga. Two types of rods predominate

both in frequency and in percentage of the microbiota in periodontosis lesions: Capnocytophaga and the Group 4 organisms of which strain Y-4 is the type s. The Gram-negative anaerobic rods which predominate in rapid periodontitis lesions include strains of Bacteroides melaninogenicus, Bacteroides capillosus, Fusobacterium strains, corroding bacteria such as Eikonella corrodens, anaerobic asaccharolytic vibrios, and strains of Selenomonas sputigena.

In animal pathogenicity studies a representative isolate of each of the five groups found in periodontosis lesions was implanted as a monoinfectant in germ-free rats, and two isolates of Gram-negative rods from rapid periodontitis lesions were also tested. All seven isolates caused periodontal disease in the gnotobiotic rats. Fourteen previously tested Gram-negative isolates had failed to show pathogenic potential. These included: Veillonella parvula, Veillonella alcalescens, Fusobacterium nucleatum, Campylobacter sputorum, Escherichia coli, Selenomonas sputigena, Bacteroides melaninogenicus, Bacteroides oralis, Treponema macrodentium, and Treponema denticola.

The histopathologic changes caused by the pathogenic Gram-negative organisms in the gnotobiotic rats were different from those induced by Gram-positive organisms. The Gram-positive organisms (Actinomyces naeslundii, A. viscosus and Streptococcus mutans) formed massive amounts of plaque, caused root caries, and led to resorption of alveolar bone characterized by a decrease in osteoblasts, but no increase in osteoclasts. In contrast, infection with the Gram-negative organisms resulted in minimal plaque and no root caries, but extensive loss of alveolar bone with intense osteoclast activity. While the case is not yet proven, the investigators feel that they are accumulating strong evidence to implicate Gram-negative anaerobes as key etiologic agents in periodontal disease. This opinion is based upon the numerical dominance of the organisms in periodontosis and in rapid periodontitis lesions, their pathogenic potential in animals, and the observation that the disease process can be halted by eliminating the organisms.

The predominant cultivable microorganism found in individual zones of pockets of two subjects with mild periodontitis were also studied at Forsyth Dental Center. Samples were taken from supragingival areas, subgingival areas, and deep subgingival areas. There was a marked difference between the supragingival and subgingival plaque. The total number of microorganisms from supragingival areas were 10 to 100 times greater than the subgingival samples from the same teeth. The subgingival flora consisted mainly of anaerobic organisms which included Peptostreptococci, Bacteroides Melaninogenicus and Actinomyces. Approximately 50% of the organisms in the supragingival plaque were Streptococcus Sanguis, whereas this organism was not abundant in the subgingival samples.

In a significance etiologic investigators at the University of Pennsylvania Center for Oral Health Research have examined the differences

between a virulent strain of Actinomyces viscosus (mentioned earlier in this report) and an avirulent strain of the same organism. This Gram-positive organism is associated with chronic periodontitis in humans, and produces periodontal disease in gnotobiotic animals, whereas the avirulent strain does not. The investigators found that the virulent form of the organism produced a carbohydrate-containing antigen which contained 67% 6-deoxytalose; and they also obtained evidence that the peptidoglycan in the walls of the virulent cells stimulated lymphocyte transformation more than did the peptidoglycan of the avirulent strain. Hence it appeared that virulence was related to several characteristics rather than to one. The investigators reasoned that these differences could not be explained by simple mutation and sought other means to explain the phenomenon. One possibility was that the Actinomyces viscosus might contain plasmids, pieces of extra-chromosomal DNA, which code for proteins and for biological activity. By this means plasmids can infect bacteria and change their characteristics and activities. For example, plasmids cause diphtheria organisms to produce a lethal toxin. To test the plasmid hypothesis, the investigators performed laboratory studies which soon provided evidence that plasmids are indeed responsible for the virulence of Actinomyces viscosus. One of the significant experiments was to cure the virulent strain of Actinomyces viscosus of its plasmid infection by treating it with a acridine orange. When cured, the A. viscosus no longer contained the plasmid, did not produce the antigen, produced cell walls with less mitogenicity, and produced less disease in gnotobiotic animals. The investigators also found that one of the Gram-negative anaerobic rods associated with periodontosis also contains a plasmid, and that other oral organisms contain plasmids. The investigators postulate that plasmid activity may underly the virulence of a number of pathogenic oral organisms.

Pathogenesis and Pathology

The exact relationship between gingivitis and alveolar bone loss is a fundamental issue which has remained unresolved for a long time. Some authorities believe that gingivitis leads inevitably bone loss, whereas others believe that gingivitis and bone resorption are unrelated. A recent study by investigators at the University of Gothenburg, Sweden, throws light on this question. In a carefully managed study, 8 beagle dogs developed gingivitis which progressed to periodontal bone breakdown, whereas 2 dogs sustained the gingivitis for 4 years without developing bone loss. This experiment suggests that gingivitis may not always progress to bone resorption and calls for additional studies to discover why some dogs were susceptible and some were resistant.

In electronmicroscopic studies at the University of Bergen in Norway on the role of dento-bacterial plaque components in the

initiation and progression of periodontal disease, attempts have been made to trace lipopolysaccharide endotoxin particles in sections of human plaque and gingival tissue. The results indicated that LPS in particulate form does not penetrate crevicular epithelium and may only be found in contact with the connective tissue when the epithelial lining is ulcerated. This finding is consistent with the idea that endotoxins cause no harm to underlying connective tissue as long as the sulcus epithelium in intact.

In studies to determine how bacterial endotoxins might instigate the inflammatory response once they gain access to the gingiva, investigators at the University of Texas showed that endotoxins caused elevation of histamine and kinin levels in dog gingiva. Their results suggest that histamine and kinins function synergistically to promote increased vascular permeability.

In another study on the role of endotoxins, scientists at Temple University have made findings with important clinical implications. In studies reported earlier, these investigators had shown that periodontally involved areas of cementum contained endotoxin. In clinical treatment it has never been possible to regain attachment of periodontal tissues in such areas. To determine if the bound endotoxin had an effect on the attachment of cells to these root surfaces, the investigators incubated involved teeth in cell cultures of gingival fibroblasts. The results showed that very few fibroblasts became attached to root which had been exposed to the disease process, whereas unexposed cementum allowed cells to attach normally. When the investigators extracted the diseased cementum with phenol to remove the embedded endotoxin or mechanically removed the diseased cementum, the cells in culture attached freely to the entire root surface. The results suggest that cementum-bound endotoxin may prevent the reattachment of periodontal tissues in humans.

In a study to determine how other periodontal plaque components may cause tissue destruction, investigators at SUNY at Buffalo have tested nonendotoxin-containing fractions of dental plaque for cytotoxic activity. They found that a soluble extract prepared by homogenizing fresh dental plaque and saline inhibited the growth of cell cultures. The active factor is thought to be a substance of molecular weight 30,000 which spontaneously aggregates in solution.

Since Gram-positive rod-shaped bacteria have been implicated in the etiology of periodontal disease and in the formation of dental plaque, studies have been made at Forsyth Dental Center to examine the role of lipids from these organisms in tissue destruction and in plaque adherence. Injections into animals of a glycolipid fraction from A. naeslundii showed tissue damage at 48 hours which included collagen breakdown and

cell destruction. Another finding was that phospholipase A prevented the attachment of A. naeslundii cells and also facilitated their removal if they were already attached, suggesting that their adherence during plaque formation is due to phospholipid.

One class of bacterial substances likely to be active in causing periodontal disease are antigens which combine with host antibody to form immune complexes within the gingival tissues, thereby initiating an immune complex disease. Immune complex diseases are defined as inflammatory diseases in which there is a continuing B-cell or plasma cell response to soluble antigens which persist in the body either because they are undegradable or because they replicate. Diseases of this type include chronic bacterial, viral and protozoan infections. Because of the predominant B-cell response in advanced periodontal disease and the strong likelihood that bacterial antigens of the periodontal plaque continually gain access to the gingival tissues and form complexes with antibody, many investigators believe that periodontal disease represents a type of immune complex disease.

To gain evidence supporting this concept, an investigator at SUNY at Stony Brook injected immune complexes into the palatal gingiva of animals, and studied the resulting ultrastructural alterations to see if they resembled changes seen in periodontal disease. He found that some features of periodontal pathology were evident, but others did not occur during the period of the experiment. One significant finding was that osteoblasts and fibroblasts showed early alterations but other cells including endothelial cells did not show changes. Although polymorphonuclear leukocytes were present in large numbers in the early phase of the lesions these cells showed no degeneration and did not release their lysosomal granules. On the other hand, mast cell rupture with spreading mass cell granules were seen two hours after injection. Initial degeneration was seen in collagen fibrils, but phagocytosis of these fibrils by fibrocytes or macrophages was not observed. Macrophages showed no alterations and osteoclastic activity was not observed. After 96 hours new osteoblasts and fibroblasts were evident and the deposition of new bone had begun.

In other studies of inflammation investigators at Duke University have made findings pertinent to periodontal disease. First they developed a method for measuring the monocyte chemotactic responsiveness, and then proceeded to establish the normal response to this test in a population of healthy humans. In later studies they tested patients with influenza and found that this virus infection depressed the monocyte-chemotactic response as much as 70%. More than 90% of these patients showed a depression of their monocyte-chemotactic responsiveness during infection. These findings were supported by animal studies in which mice with either influenza or herpes simplex virus infection showed a depressed macrophage responsiveness to chemotactic stimulation. These findings may partially explain the long observed clinical observations

that patients with influenza infections sometimes have an exacerbation of their periodontal disease during the infectious episode.

While mediators of immune inflammation have captured the attention of investigators during the past few years, a few scientists are now beginning to focus on normal physiological substances which regulate inflammatory reactions. In one study on regulation, investigators at Duke University have found that normal human serum contains a factor which suppresses the chemotactic responsiveness of monocytes. This factor appears to be an acidic, heat-stable protein which acts directly on monocytes but does not destroy the activity of chemotactic lymphokines. In preliminary studies, high levels of the inhibitory factor were detected in patients with a new syndrome characterized by marked hyperimmunoglobulinemia E, eczema, depressed delayed cutaneous hypersensitivity and undue susceptibility to infection.

In another study on immunoregulation, investigators at the University of Oregon have isolated a fraction from human serum which inhibits lymphocyte transformation induced by PHA. This effect is dose-dependent and not due to toxicity of the cells as judged by trypan-blue exclusion. Investigators are now developing a bioassay to measure this immunoregulatory material in small volumes of serum. The investigators believe that the antigenic stimulus occurring in chronic periodontal disease also brings about the formation of immune regulatory materials in the serum.

The relative importance of different immunological reactions in the pathogenesis of periodontal disease continues to be studied in a number of laboratories. While the possibility that cell mediated immunity plays a role in periodontal disease is supported by _in vitro_ studies, occasional _in vivo_ studies have produced evidence which speaks against such a possibility. In one recent study, monkeys were treated with anti-thymocytoglobulin. Subsequently, they were put on an experimental gingivitis regime and assays made of lymphocyte number and lymphocyte response to PHA stimulation. Although the monkeys treated with antithymocytoglobulin showed the expected depression in total lymphocytes and in lymphocyte function, clinically the monkeys showed the same degree of gingivitis as the control monkeys. Similar experiments were performed at Ohio State University in rice rats. In that study, cell mediated immune reactions were decreased by thymectomy and by irradiation, as shown by the migration inhibition assay and by lymphocyte transformation assays. In spite of this treatment, all rice rats developed periodontal disease in the same manner and degree as animals not subjected to thymectomy and irradiation. At the University of North Carolina, hamsters were used to test whether cell mediated immunity played a role in experimental periodontal disease. The results showed that the incidence of periodontitis in neonatally thymectomized hamsters was the same as that observed in sham thymectomized

animals. These findings from animal work suggest that cell mediated immunity may not be an important factor in the pathogenesis of periodontal disease.

Recent data from clinical studies also provides evidence against the possibility that cell mediated immunity may be important. In these studies North Carolina investigators tested organisms isolated from patients during experimental gingivitis to determine whether or not these organisms could cause transformation of peripheral lymphocytes. The results showed little correlation between blast transformation with specific plaque bacteria and developing gingivitis. Furthermore in cross-sectional studies of patients with varying degrees of periodontal disease, lymphocyte transformation with specific plaque organisms could not be correlated with disease severity.

Normal Connective Tissue Metabolism

Collagen synthesis and degradation must be carefully regulated in order to permit the development and maintenance of normally functioning periodontal tissues. To understand the basic dynamics of collagen metabolism, investigators at the University of Washington in Seattle, are precisely defining the biochemical steps involved and localizing these reactions in subcellular structures. Special efforts are being made to identify points in the biosynthetic pathway at which physiological controls are exerted. In the area of collagen synthesis, studies on the structure of procollagen, the collagen precursor, had shown earlier clearly that procollagen from bone is synthesized as a disulfide-linked protein. Findings from recent studies on organ cultures of bone, using special antibody labelling techniques to localize the procollagen, have provided evidence that microtubules may translocate the procollagen from its site of synthesis on polysomes to a site near the cell membrane. In these experiments procollagen was also observed in the cisterna of the rough endoplasmic reticulum and the Golgi elements of both cell types.

While the collagen protein has been widely studied, the ground substance components of connective tissues are also important. Not only are these proteoglycan substances believed to influence collagen fibril formation, but they are also thought to protect collagen fibrils from degradation. Thus, their metabolism may be critical in the maintenance of connective tissues. Investigators at the University of Michigan Institute of Dental Research have been successful in isolating up to 90% of the proteoglycans in connective tissues. They have studied the basic chemistry of these complexes and their interactions with other components of connective tissues, such as hyaluronic acid and link proteins. According to the Michigan scientists, proteoglycans are large macromolecules in which large numbers of sulfated polysaccharides chains are attached to a portion of the polypeptide backbone. Typically 100 chondroitin sulfate and 50 keratan sulfate changes are found for an

average proteoglycan molecule. In the extracellular matrix of connective tissues, the proteoglycans are present as large aggregated structures in which many proteoglycan molecules and smaller proteins are bound to hyaluronic acid. In recent studies, they have isolated and purified cathepsin D, an intracellular protease, which is believed to promote the degradation of proteoglycans from a wide variety of tissues in normal metabolism.

In new studies focused specifically on the normal metabolism of the periodontal ligament, investigators at two universities appear to have resolved a long standing question. Previous studies using autoradiographic labelling suggested that collagen in the periodontal ligament had a high rate of synthesis and degradation. To reexamine this question, investigators at the Center for Oral Health Research at the University of Pennsylvania measured directly the biosynthetic activity of freshly excised periodontal ligaments from human and hamster teeth. Their results indicated that the isolated ligaments did synthesize protein, but not collageneous protein. Similar results were obtained in a study of the same type on rat periodontal ligament carried out at Fairleigh Dickinson University. The results of both of these studies suggest that the collagen of periodontal ligament is quite stable and undergoes little turnover.

Collagen Metabolism in Disease

Last year's annual report described studies indicating that lymphocyte products resulting from immune interactions could damage fibroblasts, the cells which maintain the collagen structures of the gingiva. During the past year investigators at the University of Texas Dental Science Institute and Harbor View Medical Center in Seattle have brought forth evidence that a particular lymphocyte produces a substance which can cause killing of fibroblasts. These investigators separated out by EAC rosetting techniques human B-lymphocytes from patients with periodontal disease. When the B-cells were cultured with dental plaque, they produced lymphokine mediators, one of which caused direct lysis of human fibroblasts in the absence of antibody or macrophages. Since B-cells are found in large numbers in chronically inflamed gingival tissues, it seems likely that these cells may cause destruction of gingival fibroblasts and thereby reduce the rate of new collagen formation in the gingival tissues. The investigators have thus identified a specific mechanism of anabolic inhibition which may explain in part the net loss of collagen in disease.

At the Center for Oral Health Research at the University of Washington in Seattle, investigators have obtained results which appear to serve as examples of the mechanism of inhibition cited above. These scientists have shown that specimens of diseased human gingiva produce 25 to 35% less collagen than specimens of healthy tissue. This result closely agrees

with the results of in vivo studies conducted in marmosets by workers in Seattle and at the University of Texas Institute of Dental Science. In corroborating studies on individual cells by the University of Washington scientists, it was also shown that gingival fibroblasts from humans with chronic periodontitis produced abnormal collagen molecules, whereas fibroblasts from healthy tissues did not.

In related studies on collagen metabolism in disease, scientists at the University of Texas Dental Science Institute, the University of Alabama and the National Institute of Dental Research have dealt with the enzyme collagenase, which degrades existing collagen fibers. Earlier studies had established that macrophages contain collagenase enzyme in an inactive form, but these cells could be stimulated to release active enzyme and to synthesize new collagenase through cell mediated immunity mechanisms, or by direct exposure to dental plaque. In more recent studies, scientists at the University of Alabama have isolated large amounts of collagenase from bovine gingiva maintained in tissue culture. This enzyme has been found to be similar to other mammalian collagenases, including the macrophage collagenase. The bovine enzyme is also detectable in tissue culture in a latent inactive form and can be activated by biological substances, such as lymphocyte or microbial products. The Texas investigators have now performed similar studies on human gingival tissue itself and have obtained results which parallel those seen with the macrophage and bovine gingival systems. In these later studies, they removed already present active collagenase from the human gingival specimens by pretreating this tissue with reconstituted collagen fibrils. Subsequently, they activated the latent collagenase remaining in the gingival tissue by incubating the gingival tissue culture fluids with lymphocyte sonicates. This incubation resulted in a significant solubilization of collagen gel. While the exact cellular origin(s) of the collagenase in human gingiva remains unknown, these results indicate clearly that the enzymatic destruction of the collagen in gingiva can be increased by an inflammatory mechanism. Thus, the research data presented here suggests that the net loss of collagen in periodontal disease is the result of two basic phenomena: decreased synthesis and increased breakdown.

In wound healing experiments on rat palatal mucosa, investigators at the University of Southern California have obtained evidence that new collagen is first synthesized and subsequently undergoes insolubilization during a period of maturation. This process of insolubilization is unaffected by inhibitors of collagen crosslinking. Thus, the scientists conclude that maturation is not related to crosslinking within the collagen itself, but instead, is related to the interaction of collagen with non-collagenous proteins of the extracellular matrix. Since inflammed human gingiva shows a three-fold increase in soluble collagen, the investigators believe that there may be a defect in the maturation process during inflammation.

Investigators at the SUNY at Buffalo have extended the use of the Macaca speciosa monkey as a model for different periodontal conditions. In these studies adult monkeys developed dilantin gingival hyperplasia from the same dosages and time periods which cause gingival enlargement in humans. Since this type of gingival enlargement is characterized by the formation of large amounts of collagen, University of Alabama investigators have classified the types of collagen in the gingivae of patients on dilantin therapy. In addition to the collagen data, the scientists also made the interesting finding that about 20% of the protein in this gingivae is a new type of acidic noncollageneous protein.

Bone

Collaborating investigators at the University of Rochester and the National Institute of Dental Research continued their studies on the Osteoclast Activating Factor (OAF) produced by lymphocytes. Recent findings indicate that the peak production of OAF is associated with increased incorporation of amino acid into protein, but precedes the incorporation of thymidine into DNA. Thus, OAF production occurs before lymphocyte transformation. It was also shown that bone resorptive activity was consistently found in the supernates of PHA-stimulated mononuclear cells, and in the supernates of either stimulated or unstimulated B-lymphocytes. These recent results suggest that T-lymphocytes either alone or in combinations with macrophages, are not the source of OAF. To investigate whether or not OAF could act locally on bone, concentrated OAF was injected directly onto the surface of the calvarium of weanling rats each day for one week while control animals were injected with medium only. Histologic studies indicated that the OAF caused local resorption.

In previous studies it had been shown that bone resorption activity could be demonstrated in the gingiva of monkeys. To identify the active factors, investigators at SUNY at Buffalo tested gingival fragments in bone tissue cultures. By radioimmunoassay and by inhibition experiments with the specific inhibitor indomethacin, the Buffalo scientists showed that one of the active resorption factors was a prostaglandin. Their studies showed that the prostaglandin accounted for a significant portion of the total bone resorptive activity in the gingival incubation medium. Their experiments also revealed that most of the prostaglandin was synthesized in vitro.

In a study at the University of Oregon, investigators have measured the gingival concentration of heparin in male beagle dogs with different degrees of periodontal disease. In these experiments the heparin was extracted, identified by microelectrophoresis and quantified by a colorimetric method. The concentration of heparin was found to be higher in the gingival tissues of dogs with severe gingivitis and

periodontitis as compared to the gingiva of dogs with healthy or mildly inflamed periodontal tissues. This finding is of interest because heparin enhances bone resorption and collagenase activity.

In earlier studies, investigators at Forsyth Dental Center had shown that the bone loss observed in experimental rat periodontal disease caused by Gram-positive organisms appeared to be due to cessation of bone formation rather than to resorption of existing bone. In recent experiments these workers have injected constituents of the pathogenic bacterium Actinomyces naeslundii into the periodontium of rats. They found that all of the microbial fractions caused death of the osteoblasts and osteocytes, but had little effect upon other cells nearby. These results indicate that the bone forming cells are particularly susceptible to bacterial products of these organisms and supports the concept that bone loss caused by these bacteria is due primarily to cessation of new bone formation.

Investigators at Harvard School of Dental Medicine and Harvard Medical School have recently added another dimension to the study of bone resorption. Previous studies have emphasized the loss of mineral in bone resorption, primarily because there have been no methods by which the loss of organic components could be monitored. As a result of a new isolation procedure for collagenase, however, it is now possible to quantitate the collagenase released into tissue culture medium where bone resorption is taking place. Results obtained so far indicate that the amounts of collagenase produced correlated directly with the amount of bone resorption.

At the University of Missouri at Kansas City investigators have been studying specific metabolic pathways in bone to elucidate the basic mechanisms related to the growth, maintenance and resorption of this tissue. In recent efforts these workers have made two important major discoveries. They have isolated specific cell types from bone which respond to parathormone and to calicitonin, and they have discovered that parathyroid hormone exists in the parathyroid gland in man and other species as a precursor compound called proparathyroid.

In their in vitro studies of bone cells isolated free of bone matrix, the Missouri scientists first found that these cells contained a population which responded to both calcitonin and parathyroid hormone, and another population of cells which did not respond. When the responsive cells were further tested, it was found that some of these cells responded only to parathormone but not to calcitonin. A second group of the responsive cells reacted to the same extent to both calcitonin and parathormone. This second group was further studied and cells were eventually isolated that responded more to calcitonin than to parathormone. In subsequent experiments the cells most responsive to parathormone and those most responsive to a calcitonin were then cultured on solid surfaces where

they showed markedly different morphologies and appeared to be derived from different cell types in the intact bone. It is considered that these discoveries represent a major breakthrough in technology for the study of bone tissue and bone cells and opens the way for refined metabolic studies on individual bone cells.

In the parathormone studies the investigators have now elucidated by amino acid sequencing the structure of a major portion of the prohormone from several species, including bovine, human and procine glands. They are currently studying the physiology and chemistry of the conversion in the gland of the prohormone to the active hormone.

Treatment

In studies up to 3 years in length, chemotherapeutic agents have been used to eliminate the suspected Gram-negative organisms found in the advancing front of the lesions in patients with periodontosis and with rapidly destructive periodontitis. In these studies, tetracycline was given systemically at a level of one gram per day for 3 weeks and this was coupled with surgical debridement of periodontal tissues with local infiltration of tetracycline. Seven patients treated in this manner 3 years ago have shown no advance in their disease, and in addition, repeated cultures from sites of previous disease have revealed none of the suspected organisms. However, large numbers of organisms typical of chronic periodontitis have been isolated from these sites. An additional 12 patients with periodontosis have been treated in this way for periods ranging from 3 months to 1 1/2 years. These individuals have also shown no further destruction and no return of the suspected Gram-negative rod-like organisms. Similar results have been obtained in patients with rapid periodontitis and with periodontal abscesses. In some instances mobility of the teeth has been significantly decreased.

Investigators at the University of Pittsburgh and at Ohio State University worked with rice rats because these animals have a high susceptibility to periodontal disease on certain diets and therefore serve as useful models of the disease. Both sets of investigators have been able to show clearly that rice rats can be maintained free of periodontal disease by the administration of antibiotics. In one of these studies it was found that depressing the flora with an antibiotic cocktail containing 4 antibiotics in inhibited experimental periodontal disease for more than 8 weeks.

In the beagle dog study referred to earlier, the Gothenburg investigators tested the efficacy of mechanical tooth cleansing for a four year period. In animals maintained on a soft, disease producing diet, one group of dogs was subjected to meticulous tooth brushing twice each day while the teeth of the other group were not cleaned. During the four year period most of the untreated dogs

developed gingival inflammation which progressed to periodontitis, but the treated dogs did not show signs of gingivitis or periodontal breakdown. The gingival pocket depth in the untreated dogs averaged 3.4 mm in the posterior molar and premolar areas and showed a loss of periodontal fiber attachment of approximately 3 mm with an average bone loss of nearly 4 mm. The treated animals, on the other hand, showed no pockets, no loss of attachment and no bone loss. The findings from this study indicate that regular and rigid mechanical hygiene procedures can completely prevent signs of periodontal disease.

MEETINGS SPONSORED

During FY 1975 the Periodontal Diseases Advisory Committee held its sixth, seventh, and eighth meetings. Two members, Dr. Kirk Hoermann and Mrs. Patricia McClean retired from the Committee and were replaced by Dr. J. M. Goodson of the University of California and Dr. Genevieve Matanoski of Johns Hopkins University.

At its October 1974 meeting the Periodontal Diseases Advisory Committee held a discussion on the formal comprehensive evaluation of the NIDR Periodontal Diseases Program then being planned. The progress made up to that time in developing the evaluation was described and the Committee offered its opinion on several issues. The Committee then passed a motion unanimously commending the NIDR for planning to have the evaluation and urged the Institute to proceed with all due speed. Other items included a briefing on research training activities, a discussion of plans for Committee persons to visit dental research institutes and centers, a discussion on instrumentation to measure periodontal disease, and finally a discussion on approaches to disease control. The Committee recommended that a workshop on instrumentation be developed.

At its seventh meeting in February 1975, the Periodontal Diseases Advisory Committee heard and discussed progress reports on the formal evaluation of periodontal disease research activities. At that time, a contract had been let and the objectives of the program were being reviewed. Other items covered at this meeting included a report on a visit to the University of Pennsylvania Center for Oral Health, a discussion on the potential in periodontal disease research of cooperative clinical research units, and another discussion on the potential of technological forecasting. Finally a subcommittee was formed to develop a program for a workshop on instrumentation to measure periodontal disease.

At its eighth meeting, held in June of 1975, the Periodontal Diseases Advisory Committee again focused on the Periodontal Diseases Program evaluation. Reports on the evaluation indicated that the evaluating panel had already assessed individual projects and were now

preparing to evaluate program balance. The Committee also developed further its plans for an instrumentation workshop and heard a formal presentation on the cooperative clinical programs of the National Cancer Institute. In discussions on the potential application of such programs to periodontal research, the groups concluded that the task force approach may be more appropriate at this time. Finally the Committee paid its respects to the retiring chairman, Dr. Hine, and to the other retiring members, Dr. Levy and Dr. Goldman.

FUTURE PLANS

In order to maximize the possibility of developing a rational means for the prevention and control of periodontal disease, continued efforts will be made to clarify the critical steps in the disease process. Thus, ongoing and new studies will attempt to develop both practical and fundamental knowledge on all of the biological events involved in this disease from the earliest attachment of bacteria through the ensuing stage of local inflammation to the point of irreversible tissue destruction.

Now that it is known that approximately a dozen individual types of microorganisms can cause periodontal disease when implanted in germfree rats, expanded studies must be carried out to characterize these suspected pathogens and examine both immune and non-immune mechanisms by which these organisms may destroy tissues. Studies to characterize the newly discovered organisms will require microbiological experiments involving morphological, biochemical, enzymatic, nutritional, serologic, and other approaches. At the same time comprehensive studies must be done to determine the nature of the host response to these microorganisms. Thus, specific efforts will be made to initiate immunologic studies in gnotobiotic animals infected with single strains of organisms. These studies should lead to additional studies in gnotobiotic animals on the potential of protective immunization in periodontal disease, a field which has been neglected. With the new knowledge now available, studies on protective immunity are feasible, and the gnotobiotic animal system is especially appropriate for such experiments. Meanwhile clinical studies of a comprehensive nature will be developed to determine the actual role of the suspected pathogens in human disease. These studies will require the specialized talents of a group of cooperating investigators, perhaps located in different geographical sectors, who will pool their capabilities and clinical populations in a comprehensive approach to determine the role of the specific organisms in human disease. Additional etiological studies to be developed will consist of intensive exploration of the hypothesis that plasmids may account for the virulence of certain pathogenic organisms. Such studies will also utilize to the fullest a combination of in vitro,

in vivo, and clinical experiments. Insofar as treatment is concerned, both in vitro and in vivo trials of promising antiplaque agents will be encouraged. Plans are also under consideration for a scientific workshop on the current status and future potential of antibiotic agents in controlling severe forms of periodontal disease. Additional studies to develop controlled release of chemotherapeutic agents for longterm prevention of periodontal disease will also be encouraged.

SUMMARY

Since periodontal disease involves complex biological processes, the periodontal disease program supports research and research training in a wide variety of fields. During the past year the program awarded research funds of $4.2 million for 4 program projects, 74 research grants and 1 conference grant. The program also awarded research training funds of $0.83 million to support 41 trainees on 11 training grants, and to support 14 postdoctroal fellows and 4 career awardees. Contract activities involving in vitro chemotherapy studies and clinical studies on immunology consumed $0.5 million. During the year staff made visits to many institutions to program, monitor or to evaluate proposals. Staff also participated in 12 scientific meetings and 4 formal professional development courses.

Research highlights included the identification of pathogenic organisms and of a potential virulence mechanism, and findings on the role of endotoxin and immune inflammatory mechanisms in the production of periodontal disease. Also included were reports on the efficacy of antibiotics and of mechanical hygiene in prevention.

Studies on pathogenic organisms showed that 5 groups of Gram-negative anaerobic rods can be isolated from the advancing front of periodontosis. On the other hand, lesions of rapidly advancing periodontitis are populated by different Gram-negative anaerobic rods. Representative strains of the predominant organisms from both of these periodontal conditions produce severe disease in gnotobiotic rats, whereas 14 other suspected pathogens failed to cause disease. In studies on the virulence of the Gram-positive pathogenic organism A. viscosus, investigators obtained evidence that plasmids, extra-chromosomal pieces of DNA, change the bacterium to a virulent form by coding for proteins and biological activity. As a result of being infected by a plasmid, virulent strains of A. viscosus make a specific carbohydrate-containing antigen and a mitogenic peptidoglycan and cause periodontal disease in animals. The avirulent strains do not contain plasmids and do not possess these characteristics.

Research on pathogenesis and pathology dealt with the relationship between gingivitis and alveolar bone loss, the role of endotoxin, and the role of immune mechanisms. In a long-term study, gingivitis

in a majority of beagle dogs progressed to periodontal bone loss, but some dogs had gingivitis which did not lead to bone loss during the 4 year period. These results suggest that gingivitis may or may not progress to bone resorption. A Norwegian study indicated that bacterial endotoxins do not penetrate into the periodontium unless there is damage to the epithelial lining. However, in a clinically related study scientists showed that endotoxins from dental plaque become absorbed to the adjacent tooth surface and prevent the reattachment of normal healthy cells to these altered root surfaces. When the investigators removed the absorbed endotoxin, healthy cells could then attach freely to these surfaces. Thus, endotoxin may interfere with reattachment clinically.

Because of the strong likelihood that bacterial antigens continually gain access to the gingival tissues and form complexes with host antibody, some believe that periodontal disease is an immune complex disease. The presence of a strong B-cell infiltration in advanced disease is consistent with this concept. Therefore one investigator injected immune complexes into tissues to examine the effects of this treatment. The salient finding was that osteoblasts and fibroblasts showed significant ultrastructural alterations whereas other cells did not. This result suggests that immune complexes may cause inhibition of new bone and collagen formation.

In early efforts to study regulation of the immune response, investigators have found that normal human subjects have a serum factor which suppresses the chemotactic responsiveness of monocytes. The inhibitory factor was detected in high levels in a specific group of patients with high susceptibility to infection. In another study investigators detected a serum factor which inhibits lymphocyte transformation.

In studies on the importance of different immune reactions, evidence was gathered to suggest that cell-mediated immunity may not necessarily be involved in periodontal disease. In separate studies cell-mediated immunity was inhibited in monkeys, in rice rats and in hamsters either by thymectomy, or by antithymocyte globulins. Nevertheless all of the animals developed periodontal disease. Furthermore, neither patients with varying degrees of periodontal disease, nor patients developing experimental gingivitis showed any correlation between disease severity and signs of cell-mediated immunity.

Studies on normal collagen synthesis brought out further details on the biochemical and cellular dynamics involved in the formation of the collagen precursor procollagen. Other studies on normal connective tissue emphasized the proteoglycans of the ground substance. Separate studies of both animal and human specimens

showed that the collagen of the periodontal ligament is quite stable and undergoes little turnover. Studies on collagen metabolism in disease have focused on mechanisms by which the rate of collagen degradation or synthesis is altered. In one study it was shown that cells associated with humoral immunity could cause direct lysis of human fibroblasts, a finding consistent with other studies showing that diseased human and marmoset gingiva produce less collagen than healthy gingiva. In studies on the enzymatic breakdown of collagen, scientists have shown that the collagen-destroying enzyme collagenase exists in human gingiva in a latent form which can be activated directly by bacterial stimulation or indirectly via inflammatory mechanisms.

New facets of the mechanism of bone resorption continue to be unfolded. Studies on the Osteoclast Activating factor (OAF) indicate that production of OAF by lymphocytes precedes cell transformation, and that B-lymphocytes rather than T-lymphocytes may be the source of OAF. Other investigators showed that much of the bone resorptive activity in the gingiva of monkeys is due to prostaglandin. Heparin levels were found to be elevated in dogs with severe gingivitis and periodontitis, a finding of interest because heparin enhances both bone resorption and collagenase activity.

Recent research on treatment and prevention indicates that both mechanical therapy and chemotherapy have value. Mechanical and surgical treatment coupled with a concentrated regime of systemic antibiotics maintained periodontal health in seven patients with periodontosis for 3 years. New studies with rice rats produced results consistent with these findings. In a 4 year study in beagle dogs, the efficacy of mechanical hygiene was confirmed. Dogs with unbrushed teeth developed periodontal disease which included pocket formation, loss of attachment and alveolar bone loss, whereas dogs with teeth brushed twice each day showed none of these findings.

Future plans include laboratory studies to characterize organisms suspected of being pathogenic, animal studies to determine the mechanisms by which they may cause disease, and clinical studies to assess the actual importance of these organisms in human disease. Studies on the potential of protective immunization and of chemotherapy are also being planned.

Prepared by A. A. Rizzo

ANNUAL REPORT FY 1975

CRANIOFACIAL ANOMALIES PROGRAM BRANCH

INTRODUCTION

The Craniofacial Anomalies Program supports research and research training related to the detection and diagnosis, etiology, interception and habilitation of craniofacial malformations. Research is conducted in the areas of cleft lip/palate, other congenital anomalies involving facial or cranial structures, acquired disfigurements resulting from surgery or accidents, malocclusion of teeth and jaws, and the effects of anatomic malformation on oral function.

To achieve the program objectives of reducing the incidence, morbidity and mortality of craniofacial anomalies, more knowledge is required at both the basic and clinical research levels. Consequently, research funds are divided among epidemiological studies, basic investigations in developmental biology and clinical studies in growth and development and treatment.

ADMINISTRATION

Research grant support in FY 1975 was distributed among 81 research grants which included 8 program projects, 56 regular research grants, 14 special dental awards, 1 clinical research center grant and 2 conference grants for a total expenditure of 5.1 million dollars. The program also supported training in basic sciences and research related clinical areas with awards amounting to 1.57 million dollars. The program awarded $791,778 for 14 training grants furnishing stipends for 49 trainees. Under the Weinberger program, $673,692 was awarded to support 39 fellows on 7 institutional fellowship grants. Under the National Service Award program, $109,063 was awarded to support 8 fellows on 2 grants. Five career development awards were made at a cost of $111,914. In addition, $134,800 was awarded for 12 (F-32) postdoctoral fellowships, and $57,275 for 7 (F-22) postdoctoral fellowships. A total of 23 predoctoral trainees and 73 postdoctoral trainees received support.

In Table 1, the distribution of research grant support is listed according to funding mechanisms. Most research was supported through program projects and regular research grants. It is noted that Program Projects utilized 33% of available funds as compared with 57% the previous year. Table 2 illustrates the distribution of research grants by disease category. From the previous year, research funding on malocclusion has increased to 31% while funding for cleft lip/palate and Craniofacial Anomalies General remained at 35.7% and 24.4% respectively. As Table 3 indicates, funding was rather evenly distributed among studies on etiology, pathology and diagnosis and treatment.

TABLE 1. FY 1975 RESEARCH SUPPORT BY FUNDING MECHANISM

Total Active Research Grants	97
Grants awarded in FY 1975	81
Terminated or extended without funds	16

ALL GRANTS BY TYPE:		Active	Funded	Funds
Program Projects	(P01)	10	8	$1,657,289
Clinical Research Center	(P02)	1	1	337,478
Regular Research Grants	(R01)	69	56	2,916,909
Special Research Award	(R23)	15	14	143,316
Conferences	(R13)	2	2	49,330
TOTALS:		97	81	$5,104,322

TABLE 2. FY 1975 RESEARCH SUPPORT BY DISEASE CATEGORY

		No. of Grants	FUNDS Cost	Percent
I.	Craniofacial Anomalies-General*	32	$1,244,573	24.4
II.	Cleft Lip/Palate	18	1,822,883	35.7
III.	Other Congenital Anomalies	5	452,578	8.9
IV.	Malocclusion	26	1,584,288	31.0
	TOTALS:	81	5,104,322	100.0

*Basic studies in developmental biology pertinent to all types of craniofacial malformations.

TABLE 3. FY 1975 RESEARCH SUPPORT BY CLASSIFICATION

		No. of Grants	Cost	Percent
I.	Etiology	37	$1,808,317	35.5
II.	Diagnosis and Treatment	25	1,562,563	30.6
III.	Pathology	17	1,654,330	32.3
IV.	Epidemiology	2	79,112	1.6
	TOTALS:	81	$5,104,322	100.0

STAFF ACTIVITIES

During FY 1975, program staff visited 12 universities and other institutions for discussions with grantees and potential grantees about extramural research support and about current advances in the field of craniofacial anomalies. Staff presentations were made at professional meetings concurrently with three of these visits. Also, staff served as observers at five site visits for review of research grant applications.

Three workshops were initiated and organized by the Craniofacial Anomalies Program:

Workshop on Psychosocial Aspects of Craniofacial Malformations, Hilton Head Island, South Carolina, October 15-17, 1974.

Workshop on Classification and Nomenclature of Morphologic Defects, Bethesda, Md., February 10-11, 1975.

Workshop on Research Related to Orthognathic Surgery, Bethesda, Md., February 13-14, 1975.

One conference was supported by the Craniofacial Anomalies Program:

2nd International Santa Catalina Island Colloquium, "Extracellular Matrix Influence on Gene Expression," Santa Catalina Island, California, September 19-23, 1974.

Staff attended and participated in the following meetings and consulted with craniofacial researchers:

14th Annual Meeting of Teratology Society, Vancouver, British Columbia, July 7-10, 1974.

Middle Atlantic Society of Orthodontists 1974 Annual Session, Washington, D. C. October 10-13, 1974.

Conference on Evaluation of Recent Advances in Craniofacial Surgery, Chicago, Illinois, November 4-7, 1974. (Formal presentation by Dr. Christiansen).

Symposium on Determinants of Mandibular Form and Growth, Ann Arbor, Michigan, February 21-22, 1975. (Dr. Christiansen served as a Chairman).

Annual Meeting of the American Cleft Palate Association, New Orleans, La., February 26-March 1, 1975.

American Association for Dental Research, New York City, April 5-8, 1975. (Dr. Christiansen served as a Chairman).

American Association of Orthodontists, Las Vegas, Nevada, April 20-23, 1975.

A. Normal and Abnormal Development and Growth

1. Studies at the cellular and subcellular level.

The crucial event leading to a morphological abnormality of the craniofacial complex can occur at any point during development. A defect at the cellular or subcellular level may reach far beyond the synthesis of an abnormal or incorrect molecule and result in extreme disarrangements of anatomic structures. Biochemical studies of cellular function relating to craniofacial developmental biology have been focused upon the mechanisms of gene expression, cellular interactions and cell communication, and the extracellular matrix and its components.

At the University of Southern California, researchers have been studying the activation of genes for transcription and participation in protein biosynthesis. Their studies have used incorporation of the thymidine analog, 5-bromodeoxyuridine (BudR), to produce alterations in the properties and structure of chromatin. The work supports the hypothesis that BudR promotes changes in chromatin condensation, probably by modification of chromosomal-protein-DNA interactions. When BudR was administered, morphological differentiation was inhibited. The evidence suggested that BudR interfered with gene activation, thus blocking the expression of genes necessary for differentiation. Further evidence suggested that the effect was due to the binding of chromosomal proteins to BudR-substituted DNA and did not affect the biosynthesis or phosphorylation of the proteins. In other studies of genetic expression, acridine orange was used as a cytochemical marker for the identification of euchromatin or "transcriptively-active" regions of chromatin within cells. Using this technique, stem cells for pre-odontoblasts were detected in dental papilla mesenchyme derived from cranial neural crest cells.

In other studies at the University of Southern California, antigenic glycoproteins (H-2 antigens) have been demonstrated ultrastructurally on the outer cell surfaces of embryonic cells. These cell-surface antigens are expressed during organogenesis such as during tooth formation, but the biological functions of the H-2 antigens are not as yet known. The antigens have also been localized on the limiting membrane of matrix vesicles found in the interface during secondary embryonic induction (epithelial-mesenchymal interactions).

The extracellular matrix and its constitutents are also of great importance in development. For example, it was shown at the University of California at Los Angeles that when mesenchymal cells from muscle are grown on plastic or cellulose acetate membrane substrates, fibrous connective tissue cells result. However, when the mesenchymal cells are grown on a special preparation of rat bone matrix, they differen-

tiate into cartilage. This effect is believed to be induced by bone morphogenetic protein in the rat bone matrix. Current studies suggest that a chemical bond exists between collagen and the noncollagenous bone morphogenetic protein, which can be cleaved by a neutral protease. It was also shown that the thymidine analog, bromodeoxyuridine, could be used to inhibit the substratum-induced chondrogenesis.

2. Studies at the tissue level.

The morphogenesis of filiform papillae of the rat tongue was examined in an electron microscopic study at Northwestern University, where scientists are using this tissue as a model system for studies of differentiation of keratinizing epithelium. The study has also produced biochemical protein profiles which showed that oral keratinizing epithelium contains proteins rich in histidine and cysteine.

Investigators at the University of Illinois found that epithelial cells produce dentin during amphibian odontogenesis. By ^{3}H-proline labeling in adult frogs they showed that while the odontoblast is the main dentin forming cell in the amphibian, the internal dental epithelial cells form dentin in the basal regions.

At the University of Southern California, ^{3}H-tryptophane-labeling was used to study synthesis and secretion of precursor enamel proteins in newborn mouse incisor tooth organs by electron microscopic autoradiography. Two types of protein were visualized at the ameloblast-dentin matrix interface: 1) electron dense granular material, and 2) characteristic enamel matrix protein. In biochemical studies, two new proteins recently isolated from rabbit incisors are currently being used as phenotypic markers for tooth-specific epithelium.

Investigators at the University of Michigan have characterized the terminal nerve fibers in the mouse periodontal ligament in an electron microscopic study. They found that non-myelinated nerves were interspersed within discrete groups of collagen fibers and also lay in close proximity with vascular and cellular elements. Myelinated nerve fibers appeared to be associated with small nerve trunks and encapsulated endings and did not extend interstitially nor within fiber groups.

The embryonic origin and ultrastructural development of the mouse trigeminal ganglion was studied at the Universtiy of North Carolina. A non-specialized appearance was observed through the 13-somite stage.

B. Cleft lip/palate

1. Embryology

Animal studies are widely used for testing hypotheses related to the occurrence of cleft lip/palate in humans as well as for examining the basic biological processes involved in palatal shelf elevation and fusion. These studies capitalize on the fact that cleft lip/palate can be produced experimentally in animals using a variety of teratogenic compounds.

At the State University of New York, experiments are in progress on the mechanism of cleft palate production in mice by hypervitaminosis A. Up to 24 hours after administration of radioactively-labelled vitamin A to mice, 80-85% of extractable radioactivity in fetal mouse head was located in vitamin A esters, mainly in acetate molecules. Further studies are underway to identify the active form of Vitamin A.

Researchers from the University of California at Davis reported that high doses of triamcinolone acetonide induced facial malformations including cleft of the secondary palate in bonnet monkeys. The study of these animal model systems may provide information which can be related to the human defect.

One theory of palatal closure is that neuromuscular development and spontaneous embryonic movements are necessary for normal palatal shelf elevation. To gain further support for this hypothesis, investigators at Michigan State University determined the dose of diphenylhydantoin necessary to induce cleft palate in mice, and found that this dosage also depressed spontaneous muscular movements.

Another theory of palatal closure is that contractile proteins cause the movement of the palatal shelves. In support of this concept, investigators at Children's Hospital Research Foundation in Cincinnati had previously shown the synthesis of contractile proteins (actin and myosin) in the palatal processes at the time of elevation. In more recent work employing electron microscopy, they have demonstrated skeletal muscle myofibrils in the posterior end of the palate. In further work to show that contractile proteins are important, they also conducted *in vitro* experiments with pharmacologic agents that affect muscle movements. The experiments showed that drugs which stimulate smooth muscle enhanced posterior shelf rotation. The investigators concluded that cholinergic effects on both smooth and skeletal muscle structures may be involved in rotation.

A third theory suggests that straightening of the cranial base in the area of the craniopharyngeal canal results in palatal shelf elevation due to mechanical forces which are translated from the cranial base to the shelves. At the University of Michigan, an organ culture system for fetal mouse heads was developed in which this theory could

be tested. The results obtained with this system indicated that mechanical forces from the cranial base are not necessary for palatal shelf elevation.

Failure of the palatal shelves to fuse because of incomplete breakdown of midline epithelium is another mechanism which may result in cleft palate. To determine whether unfused mouse palatal shelves retained the potential to fuse after the normal time of palatal closure, investigators at Michigan State University studied mouse embryos. First they separated the shelves mechanically to prevent fusion. Then, one day after the time of normal closure, they released the mouse embryos into a bath with umbilical circulation intact. The shelves subsequently fused, showing that the potential for palatal fusion may persist beyond the time that fusion normally occurs.

To discover the mechanisms by which cortisone induces cleft palate in mice, scientists at the University of North Carolina examined cranial width. On enlarged tracings of histologic sections of normal and cortisone-treated A/J mouse fetuses, they measured the distance between the optic nerves and the maxillary width. Since distances were slightly greater in the cortisone-treated A/J fetuses, the scientists believe the increased width may be related to the formation of cleft palate in these animals.

In other work at the University of North Carolina, a histological study of palatal epithelium showed increased amounts of glycoprotein on the surfaces of the palatal processes and nasal septum. The surface glycoproteins may be involved in increasing epithelial adhesiveness prior to mesenchymal fusion. Fusing epithelium was also examined at the University of New Mexico where it was noted that glycogen is present in only small amounts in epithelium about to fuse, while it is abundant elsewhere in palatal shelf epithelium. Absence of glycogen in cells indicates cell death at the palatal margins. In studies of human embryos, the same investigator reported alterations in the region of fusion prior to contact as seen by scanning electron microscopy. Epithelial cell death was also observed at the appropriate time in mouse fetuses treated with excess vitamin A or cortisone. A "healing" process occurred in the palatal epithelium in the treated animals suggesting that fusion may be impossible if shelf contact is delayed too long.

Because the cells of the palate are derived from cranial neural crest cells, studies of the localization and migration of neural crest cells are of great interest. At the American Dental Association, it was determined that cranial neural crest cells have a morphology distinct from the mesodermal cells. With scanning electron microscopy, the neural crest cells appeared to be "bottle-shaped" with filopodia ("microspikes"). Just prior to migration a filamentous network appears and is tentatively presumed to be collagen. These studies are continuing to examine the neural crest cells and the mechanisms of migration.

2. Genetics and epidemiology.

Recent experiments at the University of Southern California have examined the roles of the maternal and embryonic genotype in cleft palate formation. When blastocysts from a cortisone resistant strain of mice were transferred to uteri of a cortisone-susceptible strain and vice versa, the frequency of cleft palate occurrence changed. These results show that maternal factors are important in susceptibility to cleft lip/palate. Moreover, the maternal factors seemed to be related to the special type of H-2 histocompatibility gene loci of the mother. At New York University, genetic studies of the major histocompatibility complex (HL-A complex) in human cleft palate families have shown atypical patterns of inheritance of the serologically detectable (SD) products of the HL-A complex. The same population studied with the mixed leukocyte culture technique also showed that individuals in affected families may also share lymphocyte-defined loci.

In continuing population studies in Hawaii, investigators at the University of Hawaii concluded that inheritance models can be effectively tested by analyzing data from high risk families with one or more parents affected with oral clefts. This data supports the idea that cleft palate is multifactorial in etiology and is not the result of single gene inheritance. On the other hand, geneticists at Columbia University arrived at a different viewpoint after analyzing pedigrees from 1,017 families. Their findings suggested to them that cleft lip, with or without cleft palate, and cleft palate are caused by a single genetic system rather than two or more genetic systems. The Hawaiian study showed that the incidence of clefts was elevated among groups with Hawaiian ancestry, but this increase was not attributable to maternal racial factors or to interracial hybridization. It was also of interest that orientals did not have a significantly higher incidence of cleft palate than caucasians.

3. Psychosocial.

It is thought that there are many limiting social and psychological influences on individuals affected with oral clefts in their encounters with society. In a study of cleft lip/palate adults at Lancaster Cleft Palate Clinic, it was found that individuals affected with clefts marry on the average four years later than controls, marry less frequently, have fewer children per marriage, and have more childless marriages. The study also produced evidence that the visibility of the defect was important in determining the degree of social limitation.

Investigators at Duke University have examined the perception of parents by adolescents with craniofacial malformations, including cleft palate. Such children perceive parents as having predominantly negative emotions and imagine a higher degree of parental apprehension

than do normal adolescents. Patients with less severe malformations perceive their parents as having greater negative emotional reactions or as being more apprehensive at their births. Cleft palate patients felt their parents had less pride in them than normal adolescents.

4. Speech

The presence of oral clefts may seriously affect the ability to speak properly. Thus, habilitative efforts include speech therapy. A group at the University of Iowa has been examining diagnositic and prognostic measures pertaining to speech in cleft palate patients. They have found that the adequacy of velopharyngeal closure (closure of the pharynx with the soft palate during speech) correlates with the success of speech remediation. At the University of North Carolina, investigators compared the speech of cleft palate adults treated by surgical correction with adults treated with prosthetic devices. The results showed no differences between the two groups. They also found that the quality of speech in cleft palate children was impaired by a tendency of these children to keep their mouths partially closed. To overcome this habit, the investigators devised training exercises to teach the children to open their mouths wider during speech. These efforts resulted in a significant improvement in speech quality.

5. Longitudinal Investigations

The longitudinal cephalometric studies of cleft lip/palate patients at the University of Iowa demonstrated that patients with isolated clefts of the palate have unique craniofacial morphology which differs from that of individuals with cleft lip/palate and also from those without clefts. In these patients, both maxillary retrusion and mandibular retrusion were evident. In addition, the cranial base of individuals with isolated cleft palate was found to be normal in relative dimensions but smaller in overall size when compared to non-cleft individuals. It was suggested that the observed differences were due to morphogenetic differences in facial patterns or to mechanically-induced compensatory growth changes associated with the local defect in the maxilla. In another study on isolated cleft palate, the influence of cleft width on facial growth was examined in two groups of subjects, one with narrower clefts and one with wider clefts. The results showed that cleft width was not a significant variable in determining growth of the face.

C. Other Craniofacial Anomalies and Syndromes.

Although they occur less frequently than cleft lip/palate, other craniofacial anomalies may be much more severe and may present greater obstacles to habilitation. To make data on the anomalies more accessible to researchers and clinicians, a national collaborative data bank is being established at the University of Illinois. By pooling and analyzing data, it is hoped that better diagnosis and more successful treatment

measures will be developed.

At the University of Washington, a classification of cyclopia on the basis of the overall pattern of anomalies was devised for the purpose of studying the genetic inheritance of the different types of cyclopia. It is now possible to counsel families with a cyclopic offspring about their statistical likelihood of having another cyclopic infant. It was also reported that the genetic mutation in Apert Syndrome, a type of acrocephalosyndactyly, is associated with increased father's age at the time of conception. Moreover, there may be an increased risk of congenital heart disease and also an unusual distribution of skin lesions in Apert syndrome. In a biochemical study, also at the University of Washington, it was found that mitochondrial oxidative energy formation may be defective in human achondroplasia. Information such as this on the molecular basis of disease could potentially result in new treatment methods.

Patients with hemifacial microsomia and oculoauriculovertebral dysplasia (Goldenhar's syndrome) were examined at the University of Illinois. They were divided according to mandibular and auricular deformity and subdivided according to the severity of mandibular hypoplasia and microtia. The investigators proposed that the two syndromes are in actuality variations of the same syndrome complex. The prevalence of vertebral anomalies and epibulbar dermoids suggested that these anomalies are part of the primary defect.

Longitudinal postoperative evaluations are being made of surgical procedures for the habilitation of craniofacial syndromes at New York University. Some of the syndromes under study are unilateral and bilateral facial microsomia, craniofacial dysostosis, orbital hypertelorism and microanophthalmos. These critical evaluations may lead to modifications of established techniques and development of new surgical measures. For example, a conjunctival approach was worked out for fractures of the orbital floor and a midface degloving procedure was developed for midface fractures for craniofacial osteotomies and for placing onlay bone grafts.

The pathology of the various syndromes continues to be studied. In hemifacial microsomia, for instance, it was found that the temporal bone may be malformed and there may be hypoplasia and under-development of other structures. In one autopsy sample, the facial nerve was totally absent in the temporal bone except for its nervous intermediate component. The use of computerized axial tomography, a radiographic technique that permits imaging of the brain, its ventricles and orbital contents, is being evaluated at New York University. The technique seems to have several advantages: 1) unsuspected abnormalities may be detected, 2) the precise anatomy of an encephalocele or configuration of an abnormal orbit is of help in planning surgical approaches, and 3) post-operative complications can be detected.

D. Malocclusion

1. Craniofacial growth

For teeth to be aligned properly, tooth size must be closely correlated with jaw size. Consequently, the factors determining tooth size are important in the development of normal occlusion. The inheritance of tooth size was studied in the Eivo population of the Solomon Islands by a geneticist from the University of Connecticut. He found that the mesiodistal and buccolingual dimensions are controlled by independent genetic influences. For example, the buccolingual diameter of the mandibular first molar appears to be determined by an additive gene which accounts for 73% of the total variation, while the mesiodistal diameter of the mandibular second molar is determined by a different gene which is dominant. Larger sizes are determined by the recessive allele.

A biracial study of the maxillary midline diastema by investigators from Meharry Medical College showed that the highest prevalence of the diastema was found at the 8 year age level and generally was higher in black children than in white children.

In primate studies at the University of Washington, the effects of extraction of teeth on dental and facial development were studied. In macaque monkeys, extraction of the first deciduous molars in early mixed dentition accelerated eruption of permanent bicuspid successors and was accompanied by less mesial drift of the first permanent molar on the extracted side. When unerupted teeth were enucleated, teeth drifted mesially toward the enucleation site but there was no significant effect on skeletal growth.

A histologic study of the prenatal development of the temporomandibular joint in macaque monkeys was conducted at the University of Washington. Histologic changes were found in the meniscus of the temporomandibular joint when Meckel's cartilage regressed to the point that it no longer served as an articulation and support for the developing mandible. The changes seemed to be related to the new functional burden on the joint. Another project investigated aging changes in the human frontozygomatic suture. It was found that facial sutures fuse much later than anticipated. This may be of significance in orthodontic treatment since therapeutic remodeling of facial sutures by means of mechanical forces can probably be accomplished during a much longer period than was previously assumed.

Since the anti-cancer drug, fluorouracil is sometimes administered to young patients by oncologists, its effect on the growth of the cranial base in newborn mice was investigated at the University of Michigan. Fluorouracil treatment resulted in narrower synchondroses and in thinner occipital and sphenoid bones. Thus differentiation of cranial synchondroses may be impaired by anti-cancer drugs.

The problems of mapping skull changes with time have been difficult because there has been no accurate system for making three-dimensional measurements of the skull routinely from radiographic films. At the University of California at San Francisco, a stereometric x-ray apparatus is being developed for increasing the reliability of locating landmarks in three dimensions.

At the University of Michigan, scientists carried out cluster analysis on selected craniofacial measurements from 308 children and derived five categories of skeletal facial types. They found that the morphologic features of each category were quite specific, and predicted that the system may have future use for classifying population subgroups by facial morphology.

2. Biochemical and Cellular Aspects

Investigators from the University of Pennsylvania have been studying specific cellular biochemical changes around erupting, resorbing and moving teeth. They have devised a method for extraction of the nucleotide, cyclic adenosine 3',5'-monophosphate (cAMP) from bone which permitted measurement of cAMP levels in bone samples. The same group developed a technique for localizing cAMP within cells using immunohistological methods. They showed that osteocytes, osteoblasts and periodontal ligament fibroblasts contained cytoplasmic cAMP. In parathyroid hormone-treated kittens, the number of reactive bone cells markedly increased. Also, the presence of cAMP was determined in strategic areas around erupting teeth, suggesting that this nucleotide is involved in cellular activities related to tooth eruption. They also demonstrated microscopically that increased cellular cAMP activity is found in specific areas of the periodontal ligament and bone close to teeth during orthodontic tooth movement. Little activity was seen in neighboring zones of bone.

3. Orthodontic treatment appliances and biomechanics

The effects of extraoral high-pull headgear on the craniofacial complex was studied in macaque monkeys at the University of Washington. A force of 700 grams on each side resulted in a skeletal and dental change from normal occlusion to mandibular prognathism. This alteration was accompanied by posterior displacement of the maxilla due to bone resorption occurring at all maxillary articulations, increased flexure of the cranial base angle, and upward rotation of the mandible. Distal movement of mandibular teeth accompanied the maxillary movement and temporomandibular joint remodeling was observed. From the clinical standpoint, it is significant that the changes were maintained during growth in the posttreatment period.

At the University of Connecticut, a model system is being developed for measuring the stress-strain characteristics of the periodontal ligament. The method uses laser interferometry to measure minute

tooth displacement and piezoelectric crystal strain gauges for force calibration. When a mathematical model is developed that is capable of predicting tooth displacement, orthodontists will be better able to determine the optimum forces used in appliances.

4. Orthognathic surgery

The correction of a maxillary-mandibular skeletal disharmony may require a surgical approach if the discrepancy is severe. Problems of maintaining an adequate vascular supply to bone segments become especially important when major nutrient vessels are disrupted such as during total maxillary osteotomy. Microangiographic and histological studies in monkeys at the University of Texas showed that palatal mucosa and labial-buccal gingiva provide an adequate nutrient pedicle for single-stage total maxillary osteotomies. Minimal transient vascular ischemia, minimal osteonecrosis and early osseous union were observed. At the University of Minnesota, radioactive labeled microspheres were used to show that blood flow was reduced in osteotomized maxillary segments in dogs. However, flow was increased in palatal mucosa.

New methods of controlling vascularization may develop from other studies of vascular regulation at the University of Southern California. Embryonic cornea, cartilage, and dentin produce avascular areas when placed on chick chorioallantoic membranes. A fraction has been isolated from cartilage which inhibits vascularization when added to other tissues. Such inhibition capability could be extremely useful in therapy for retarding tumor growth or in selected instances following surgery.

Investigators at the University of Texas showed that the zygomatic buttress and pterygomaxillary suture areas offer the greatest resistance to rapid palatal expansion by orthodontic appliances. To address this problem, they showed that selected surgery significantly improves movement of the maxillary bones by palatal expansion appliances.

MEETINGS SPONSORED:

1. Psychosocial Aspects of Craniofacial Malformations, Hilton Head Island, October 15-17, 1974. This meeting brought together social scientists and dental researchers who examined the psychosocial impact of craniofacial disfigurement. Consideration was given to topics such as self-concept, body-image, desire for treatment, and research methodologies as they relate to craniofacial anomalies.

Recommendations:

a. Craniofacial malformations should be comprehensively defined to include psychosocial and cultural criteria.

b. Methods need to be developed for assessing treatment need on the basis of measurable psychosocial criteria.

c. The magnitude of the national health problem requires investigation.

d. A system is needed for dealing with treatment requirements on a national basis.

e. Means should be developed for evaluating the effects and the effectiveness of treatment from a psychosocial standpoint.

2. Classification and Nomenclature of Morphological Defects, Bethesda, Md., February 10-11, 1975. A group of experts in the identification and classification of birth defects was assembled to discuss the nomenclature and classification of malformations. The recommendations and guidelines of this workshop were published in Lancet, March 1, 1975.

Recommendations:

a. It was hoped that the guidelines proposed at this workshop would be observed in future naming of patterns of malformation, and that consideration would be given to incorporating the proposals in the next revision of the International Classification of Disease.

b. New methods in taxonomy may be advantageously applied in the analysis and classification of birth defects.

3. Research Related to Orthognathic Surgery, Bethesda, Md., February 13-14, 1975.

Recent advances and current challenges in the field of orthognathic surgery were assessed by a group of expert clinical and basic researchers in orthognathic surgery. Future clinical research directions pertaining to orthognathic surgical patients were evaluated with special emphasis on diagnosis of craniofacial malformations, selection of surgical procedures, application of orthodontic therapy and evaluation of treatment.

Recommendations:

a. A primary area of needed research concerns the prediction and control of craniofacial growth. A better understanding of the sequence and mechanisms of craniofacial development would aid in surgical diagnosis and treatment planning.

b. Basic studies in hemodynamics, neuromuscular physiology, and bone regeneration and bone grafting may stimulate the development of more effective surgical procedures.

c. The field of bioengineering has much to offer in the development of new treatment methods.

d. Complete post-operative evaluation and follow-up of orthognathic surgical patients is critical for evaluating the long-term effectiveness of orthognathic surgical techniques.

4. Extracellular Matrix Influences on Gene Expression, Santa Catalina Island, September 18-24, 1974.

The Second Catalina Colloquium continued the discussion and interpretation of advances on the molecular biology of extracellular matrices and their epigenetic influence upon differential gene expression. The proceedings of the symposium were published by Academic Press in 1975.

Recommendations:

a. Studies of transcriptional, translational, and post-translational regulation during development should be initiated.

b. Studies are needed relating the structure and function of cell surfaces in relation to cellular communication.

c. The identification and characterization of extracellular matrix molecules in both normal and abnormal developmental systems would provide clues about the nature of abberrations in the developmental processes.

d. The process of mineralization should be examined in relation to the extracellular matrix and genetic expression.

e. To aid in identifying areas of research for program development a summary document was prepared from specific research and programming recommendations made at the 27 workshops conducted by the Craniofacial Anomalies Program between 1967 and 1975. Over 500 experts were directly involved in these workshops which covered the following research areas: craniofacial growth, general anomalies, cleft lip and cleft palate, surgery, speech, occlusion, molecular biology and genetics.

FUTURE PLANS

The Craniofacial Anomalies Program (CAP) will continue to support individual research projects as well as developing and improving the Cleft lip/palate and the craniofacial anomalies centers in order to achieve a comprehensive and cohesive effort in the investigation, prevention and habilitation of deformities of the oral cavity, face, and cranium. Fundamental research efforts will be made to define the factors responsible for inducing normal and abnormal development. Specifically, the CAP will intensify its support in the field of neural crest cell migration and intercellular interactions to

better understand the critical mechanisms of craniofacial development. New surgical techniques which have recently been employed to habilitate certain craniofacial anomalies will continue to be evaluated and perfected to make available improved treatment of deformed individuals. The use of therapeutic forces to control and guide craniofacial growth and development will be explored on animal model systems and assessed through research grants, and contracts. Experimental animal model systems, including subhuman primates and rodents, will be used to study teratogenesis of cleft lip/palate. These studies will focus on the activity of enzymes, drugs, and environmental factors on palatal closure.

Contractual programs will be initiated in three areas: to study high risk cleft lip populations prospectively; to examine the interactions of the neuromusculoskeletal systems on craniofacial surgery on subhuman primates; and to address the psychosocial problems of malocclusion. The workshop recommendations will continue to be considered for implementation, and the CAP research strategy will continue to be developed.

SUMMARY

The Craniofacial Anomalies Program supports basic and applied research related to normal and abnormal growth of oral structures, the face, and the head. While it would be desirable to discover measures for the prevention of craniofacial malformations, the current lack of knowledge about the etiology and mechanisms of formation of congenital craniofacial defects makes such an approach generally not feasible at this time. Consequently, the program not only seeks to expand the understanding of the causes of craniofacial anomalies through etiological research support in basic science areas, but also hopes to improve the habilitation of persons afflicted with malformations of the head and face by means of research support in clinical treatment fields. In FY 1975, 5.1 million dollars were expended to support 81 research grants. The funds were distributed between studies of etiology (35.5%), diagnosis and treatment (30.6%), pathology (32.3%), and epidemiology (1.6%).

New developments in the growth and development of craniofacial structures have been reported in studies at the cellular level. In electron microscopic studies of gene expression, stem cells for pre-odontoblasts were detected in dental papilla mesenchyme derived from cranial neural crest cells by using acridine orange as a marker for identifying "transcriptively-active" areas of chromatin within cells. Studies of intracellular communication during development demonstrated that H-2 histocompatibility antigens are expressed on the outer cell surfaces of embryonic mouse cells during tooth formation. Further evidence was also obtained on the role of extracellular matrix in the differentiation of cartilage. Modification of bone matrix with various treatments, including enzymatic digestion with collagenase, showed that the morphogenetic protein which induces cartilage formation in vitro is probably chemically-bonded to collagen.

Cleft lip/palate formation has been studied in a variety of animal model systems. The discovery that high doses of triamcinolone acetonide will induce facial malformations including clefts of the secondary palate in monkeys gives researchers a new primate model for oral clefting. In studies related to the role of fetal neuromuscular activity in palatal shelf rotation, it was determined that doses of diphenylhydantoin which produced cleft palate in a high percentage of mouse offspring also reduced spontaneous muscular movements. Palatal shelf elevation was also studied in vitro. Contractile proteins were detected in palatal processes and pharmacologic agents affecting muscle contractility were found to enhance posterior palatal shelf rotation. The data suggest that muscle structures may be involved in palatal shelf elevation. Histological studies of fusion showed that glycoproteins present on the palatal epithelial surfaces may increase epithelial adhesiveness prior to epithelial breakdown and fusion. Fusing epithelium was also found to contain only small amounts of glycogen, making absence of this substance a good histologic marker for cell death. Scanning electron microscopy showed that alterations occur in palatal epithelium even before contact of the shelves occurs.

Human studies in the genetics of cleft lip/palate have showed that certain loci such as the major histocompatibility complex and some lymphocyte-defined loci, may be inherited atypically in cleft palate families. In an analysis of family pedigrees, the data suggested that cleft lip with or without cleft palate and cleft palate are caused by a single genetic system rather than two genetic systems. Oral clefts were found to affect many aspects of daily life. Individuals with clefts marry later and have fewer children than non-cleft palate people. Also, the parents of a child with an oral cleft may be psychologically reluctant to take pride in or care for their child in relation to the severity of the cleft as they perceive it.

Information processing in the area of craniofacial anomalies is of great interest currently. A national collaborative data bank for craniofacial anomalies is being established for the purpose of making specific diagnostic and treatment information available to researchers and clinicians. A classification of cyclopia on the basis of accompanying malformations has made it possible to counsel families on the statistical likelihood of having another cyclopic infant. Also, on the basis of the prevalence of other malformations, it was proposed that hemifacial microsomia and oculoauriculovertebral dysplasia (Goldenhar's syndrome) are variations of the same syndrome complex. The habilitation of craniofacial anomalies is being evaluated in longitudinal studies. It is hoped that better treatment will result from critical post-operative assessments of presently used surgical techniques.

Progress was made in understanding the interplay between genetic and environmental factors involved in the growth of the face and skull. Independent genetic influences were detected for mesiodistal and buccolingual tooth dimensions. Gene loci were determined which accounted for much of the variation in tooth size. The prevalence of the maxillary midline diastema was also studied and was found to occur more often in black children than in white children. A study of the prenatal development of the temporomandibular joint

showed that histologic changes in the meniscus of the temporomandibular joint resulted from new functional stresses as Meckel's cartilage regressed and no longer served as a mandibular articulation. Fluorouracil, a cancer chemotherapeutic agent, was found to inhibit the growth of the cranial synchondrosis and consequently may adversely affect craniofacial growth if given to young individuals.

Advances in the field of research on malocclusion were reported by investigators examining cellular aspects of tooth movement, changes in cranial anatomic structures during orthodontic treatment, orthodontic force systems, and blood flow problems in orthognathic surgery. A method was developed for biochemically measuring the level of cyclic adenosine 3',5'-monophosphate (cAMP) in bone and also for localizing the nucleotide within the cell using an immunohistological technique. Increased cAMP activity was found around specific areas of erupting and orthodontically moving teeth. In clinical orthodontic treatment, extraoral headgear appliances are often used to produce changes in the position of the maxilla and in the occlusion of the maxillary teeth. In a primate study of the effects of high pull headgear, it was found that other cranial structures were also affected including the cranial base, the mandible, and the temporomandibular joint. A model system is being developed for measuring the stress-strain characteristics of the periodontal ligament and for predicting tooth displacement during orthodontic treatment. The method uses laser interferometry to measure tooth displacement and piezoelectric crystal strain gauges for force calibration. Since the surgical correction of malocclusion may affect blood flow to bone segments, the design of the surgical procedure is important in determining the overall success of the operation. Investigators found that palatal mucosa and labiogingival mucosa provide an adequate nutrient pedicle for total maxillary osteotomies. It was also determined that selected maxillary osteotomies will significantly expedite movement of the maxillary bones during treatment with maxillary expansion orthodontic appliances.

Prepared by R. L. Christiansen
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ANNUAL REPORT FY 1975

RESTORATIVE MATERIALS PROGRAM

INTRODUCTION

Since the highly specialized tissues of the oral-facial complex cannot replace themselves when they are lost, due to disease, accidents, or age, there will always be a need for materials to repair these tissues in order to restore both function and esthetic appearance. Therefore, the principal objective of the Restorative Materials Program is to develop new, improved, less costly materials for better treatment of dental and oro-facial disorders. The second objective is to develop materials and devices for the prevention of oral diseases. To achieve these objectives, research support by both grant, and contract mechanisms is furnished to a variety of investigators in the physical and biological sciences.

The Program supports research in five broad categories: (1) filling materials, including alloys and composites for repairing damaged teeth, (2) bonding agents, including adhesive coatings and cements for protecting the surface of teeth against decay and for sealing the margins of fillings, (3) maxillofacial prostheses for replacing tissue defects resulting from birth defects, surgery or accidents, (4) tooth implants to provide replacements for missing teeth or anchors for bridges and dentures, and (5) miscellaneous studies on toxicity, standards, equipment, and devices designed to improve dental care.

ADMINISTRATIVE

Table 1 shows the distribution of funds for research and research training in FY 1975. The Program supported 56 research grants for $1.9 million, 5 contracts and one interagency agreement for $0.7 million. For research training the program made awards totalling $0.5 million to support 7 training grants which provided stipends for 34 trainees. The largest amount of funds were expended in implants, prostheses and restorative filling materials, about 25% in each area, the same levels as last year. We have increased the budget in the preventive area to about 9%.

Even though there is a disparity in the distribution of funds in the different areas when only grants are considered (see Table I), we have attempted to balance the program by awarding contracts in some selected areas like bonding agents, prostheses and implants.

RESTORATIVE MATERIALS PROGRAM

Program Area	No. of Projects	Obligated Funds	% of Funds
GRANTS*			
Filling Materials	17	595,000	29
Bonding Agents	2	68,400	3
Prostheses	12	451,200	23
Implants	11	401,600	20
General Studies	11	198,000	16
Prevention	3	240,600	9
Subtotal	56	1,954,800	100
CONTRACTS			
Bonding Agents	1	227,600	35
Prostheses	2	147,100	22
Implants	3	279,600	43
Subtotal	6	654,300	100
GRANTS AND CONTRACTS			
Filling Materials	17	595,000	22
Bonding Agents	3	296,000	11
Prostheses	14	598,300	23
Implants	15	681,200	25
General Studies	10	198,000	12
Prevention	3	240,600	7
Total	62	2,609,100	100
TRAINING			
Grants	7	499,270	
Fellowships	2	27,300	
Career Development Awards	2	50,000	

TABLE I

*Eight of the 56 grants were active but received no funds during FY 75.

STAFF ACTIVITIES

Program staff visited the following institutions for the purpose of programming, monitoring, or evaluating research grants, research training grants or contracts. In addition, staff participated in 18 scientific meetings, 2 of which were partially supported, and 2 of which were sponsored by us. Through these professional activities, staff was able to keep abreast with the recent developments and to help define future directions for research progress in dental biomaterials. A list of these activities is given below.

A. Dental School Visits

Columbia University, New York	Sep 1974
University of Nebraska, Lincoln, Nebraska	Oct 1974

B. Site Visits - Grant Applications

(1) Training:

Univ. of Virginia, Charlottesville, VA	Nov 1974
Georgia Inst. of Tech., Atlanta, GA	Feb 1975

(2) Programming and Research:

Univ. of Oregon, Portland, OR	Oct 1974
Emory University, Atlanta, GA	Oct 1974
George Washington Univ., Washington DC	Nov 1974
American Dental Assoc., Gaithersburg, MD	Nov 1974
Univ. of Virginia, Charlottesville, VA	Nov 1974
Univ. of Maryland, Baltimore, MD	Dec 1974
Univ. of South Carolina, SC	Dec 1974
Medical College of Georgia, Augusta, GA	Dec 1974
Univ. of Alabama Dental Sch., Birmingham, AL	Feb 1975
Emory University, Atlanta, GA	Feb 1975
Univ. of Florida, Gainesville, FL	Feb 1975
Georgia Inst. of Tech., Atlanta, GA	Feb 1975
Harvard University, Boston, MA	Mar 1975

C. Site Visits - Contracts

Nat. Bureau of Standards, Gaithersburg, MD	Nov 1974
Clemson Univ., Charleston, SC	Dec 1974
Medical College of Georgia, Augusta, GA	Dec 1974
Southern Research Inst., Birmingham, AL	Feb 1975
Univ. of Florida, Gainesville, FL	Feb 1975
Harvard University, Boston, MA	Mar 1975

D. Meetings and Conferences

Gordon Research Conference, Bones & Teeth, Meriden, NH	Jul 1974
American Chemical Society, Atlantic City, NJ	Sep 1974
American Dental Association, Washington, DC	Nov 1974
AADR, New York City, NY	Apr 1975
ADA Council on Dental Materials & Devices, Chicago, IL	May 1975
Biomaterials Symp., Gordon Rsch, Conf., Santa Barbara, CA	Jun 1975

E. Meetings Partially Supported

Symposium on Interfacial Dynamics of Cutting in Dentistry held in conjunction with AAAS, New York, New York	Jan 1975
7th International Symposium on Biomaterials, Clemson University, Clemson, SC	Apr 1975

F. Sponsored Meetings

Planning Session on the Relevance of Biomedical Engineering to Dental Science, Bethesda, MD	Mar 1975
Principal Investigators Workshop of NIDR Tooth Implant programs, New York, NY	Apr 1975

RESEARCH HIGHLIGHTS

Significant advances have been made during FY 1975 in our knowledge of biomaterials both in basic and clinical areas. The following text will briefly identify some of these advances in (1) restorative filling materials, (2) bonding agents, (3) implants, and (4) maxillofacial prostheses.

Restorative Filling Materials

The basic formulation of all of the composite filling materials on the market is the result of discoveries made by the NIDR supported research of the American Dental Association's Research Unit at the National Bureau of Standards. The composite resins are esthetically more pleasing than amalgam and are used for anterior restorations. However, they do not as yet have sufficient mechanical strength for use in posterior restorations. A novel class of reinforcing fillers is being studied which, according to theory, should not only give

adequate radiopacity to the composites but should also give dramatically improved bonding between the filler particles and the resin. Furthermore, the new filler materials are less toxic than currently used preparations. This promising work should also provide important data on the susceptibility of composites to erosion and abrasion under oral conditions.

In a clinical evaluation done at Emory University, composite dental restoratives were compared with amalgam in Class I and II restorations and with silicate in Class III, IV, and V anterior restorations. In the Class I restorations, glass-filled and quartz-filled composite materials were compared with traditional amalgams over a four year period. In the Class II restorations, the quartz-filled composite was compared with the amalgam for three years. The last study compared a composite with a silicate in Class III, IV, and V restorations for three years. Amalgam proved superior to the composites in its ability to retain its anatomic form, while the composites tend to be superior in marginal adaptation. This study also showed that the composite performed better than the silicate in maintaining anatomic form and in marginal adaptation. Gross surface deterioration, although evident, was less characteristic of the composite than of the silicate. Caries recurrence was not a problem associated with any of the three materials. This finding not only serves as a clinical exoneration of composite resins but also focuses attention on the degree and importance of the problem of microleakage. Finally, anticipated fractures never manifested themselves as a clinical problem for either amalgam or the composites.

A concurrent long-term clinical study, also by the group at Emory, assessed the degree of amalgam corrosion found when the amalgam had been placed adjacent to gold inlays, and conversely, when inlays were placed adjacent to amalgam restorations. The preliminary data indicates that the anticipated corrosion, as a result of either placement sequence (gold/silver or silver/gold), did not occur on surfaces that were polished. However, unpolished amalgam surfaces did appear to be discolored.

There has been no generally accepted way of measuring the resistance to wear of materials used by dentists to fill cavities. Many laboratory wear test procedures have been reported but the results of these tests often do not correlate well with long term clinical observations. Recently, however, investigators at the National Bureau of Standards have designed an apparatus to determine the wear durability of dental restorative materials in the laboratory. This device measures the resistance to wear of restorative materials under stimulated human oral conditions. Preliminary data indicate that testing a restorative material in this apparatus for approximately 24 hours gives results which are comparable with data obtained from several years of clinical testing. This wear-generating measuring instrument has great potential for accelerating the development of new and better dental restorative materials, because it offers a way to test new and promising materials

quickly. In this way, long term expensive clinical evaluations can be held to a minimum.

Bonding Agents

New approaches are being taken by investigators of the American Dental Association Health Foundation at the National Bureau of Standards to improve the bonding of pit and fissure sealants to teeth as a preventive measure against carious lesions. Currently an acid etching technique is used to adhere the sealant firmly to the tooth structure. The ideal method of getting a permanent adherance of the sealant to the tooth would be by chemical bonding. Investigators at NBS are trying to mordant the enamel surfaces with transition metal ions such as copper and chromium which in turn will be coupled to the comonomers of the sealants or composite resins. In preliminary studies they showed that various metal ions (mordants) absorb on the surface of hydroxyapatite, and in subsequent studies, the scientists have examined the adsorption characteristics of comonomers of the sealants to the mordanted hydroxyapatite surfaces.

The research unit at the NBS has also discovered a novel class of fluoride-containing methacrylate monomers or acrylate compounds which are capable of releasing fluoride ions when exposed to moisture. The rate of fluoride ion release when compounds of this type were immersed in water over a prolonged period was measured as a function of the copolymer composition and was found to be of sufficient concentration to give added protection to the tooth surface. If mechanical properties prove suitable, incorporation of one or more of these compounds into pit and fissure sealant resins might be of benefit in reducing the incidence of carious attack on the surrounding hard tooth tissues.

Implants

Studies related to two aspects of implants are being pursued vigorously. In one area of concern, investigators at Harvard, University of Florida and Clemson University are assessing the comparative merits of a wide variety of materials, including plastics (polymethyl methacrylate or PMMA), ceramics (alumina and bioglass), metal (vitallium and titanium alloys), vitreous carbon, and combinations of PMMA and vitreous carbon. Scientists at the above institutions are also evaluating different designs of the implants in various configurations such as cylindrical designs and replicas of the natural tooth root.

Free standing (not splinted to adjacent teeth) cylindrical titanium implants in baboons have been shown to survive for a period of 29 months by investigators at the University of Illinois. When crowns were placed

on these implants, the crowns remained in good occlusion with the opposing natural teeth. Of a total of 169 implants, 105 are still in place and function properly.

Investigators at the University of Florida have discovered another material of high promise, a bioglass ceramic. Implants of this material were fabricated in the configuration of a natural tooth root and inserted into the jaws of baboons. Initial histological data from these studies indicate that tissues adjacent to the implants are similar in some characteristics to tissue adjacent to natural teeth. Past investigations with this bioglass material indicate high promise of this material not only for use as a tooth implant, but also for other medical implant devices such as those used in orthopedic and craniofacial applications.

Maxillofacial Prostheses

At the present time there is no ideal material for the fabrication of prosthetic maxillofacial devices. However, two materials currently under investigation have shown promise; silphenylenes and terpolymers.

The silphenylene polymers, originally developed by Southern Research Institute for NASA for use in outer space, are chemically related to the commonly used silicones but are stronger and tougher. Silphenylene prostheses can be prepared in stone molds at room temperature and can be colored to various racial hues and tones with oil-ground artists' colors. Most importantly these prostheses give a more life-like appearance than currently used materials.

Investigations at George Washington University have shown that a terpolymer mixture of three common organic monomers undergoing emulsion polymerization can yield an elastomeric film which may be cast from the latex in gypsum molds. Prostheses made from this material have exhibited good tensile strength, staining characteristics and weatherability, and remain flexible to -20°C.

Since a large number of commercial plastics are available from many chemical companies, investigators at Union Carbide are screening a number of these for their potential use as a prosthetic material.

Investigators at the University of Michigan have shown that alloys used for partial denture clasps need not have great tensile strength to keep the clasps from breaking. Recent evidence indicates that if the ductility of the alloy is sufficiently high, clasps do not fracture. In addition, it has been shown that small amounts of other nonprecious metal additives increase further the ductility, the elongation and tensile strength of these alloys.

MEETINGS SPONSORED

During the year the program supported two important symposia, organized a planning session for a workshop on biomedical engineering and held an informal conference on implants.

A grant was awarded to Clemson University to partially support the 7th International Biomaterials Symposium, which brought together basic and clinical researchers in reconstructive, plastic, maxillofacial, cardiovascular, orthopedic and oral surgery, as well as general surgeons and dentists. The Program also provided partial support for the Symposium on Interfacial Dynamics of Cutting, (held in conjunction with 1975 meeting of the American Association for the Advancement of Science in New York City), which brought together scientists from diverse fields at a common forum to examine and evaluate new information that is emerging in such fields as interfacial thermodynamics, interfacial adhesion and cohesion, chemical alteration of the characteristics of interacting media, industrial engineering and deep-rock drilling. Such information has important bearing on the cutting and drilling problems of dentistry and will facilitate the efforts of scientists in dentistry and in other disciplines to develop fundamental concepts and understanding of this problem.

Program staff also organized a planning session for a workshop on the relevance of biomedical engineering to dentistry." At this meeting consultants from biomedical engineering, orthodontics and clinical dental investigators discussed how the rapid developments in biomedical engineering area could help in developing better instrumentation in preventive diagnostic and therapeutic dentistry, and how more fruitful collaborative efforts could be fostered.

At the informal meeting on tooth implants held in conjunction with the American Association of Dental Research meeting in New York City, contractors and grantees reported their latest findings and discussed future prospects for tooth implant research.

FUTURE PLANS

With the new methods now available to eliminate the undesirable gamma 2 phase in amalgams, it may be possible to increase the longevity of these restorations. Preliminary clinical and laboratory evaluations tend to confirm the initial claims that these new amalgams are less corrosive and less prone to marginal fracture and, thus, they may provide an improved health measure of significance. To obtain more convincing long-term clinical data, program staff will encourage and expedite the additional clinical evaluations.

There is a continuing effort to improve mechanically and esthetically the composite resins for both anterior and posterior restorations. Developments of newer filler materials offer an opportunity to increase the strength of composite resins. Thus, research for new and better filler materials for composite resins as posterior restoratives will be of high priority.

Since the time honored and successful methods of casting employed to fabricate prostheses of gold alloys are not always applicable to the newer non-precious metal alloys currently used, we will initiate collaborative research efforts to develop new equipment and casting techniques that would be appropriate for newer non-precious metal alloys.

Because of the increase in the price of gold, the dental gold alloys are becoming prohibitive for routine use. Also, the supply of essential raw material for other alloy systems may become uncertain because of political instability in many of the countries supplying these materials.

Therefore, we plan to initiate a targeted research effort to find alternative alloys not containing gold or other precious metals to avert a possible crisis in restorative dentistry.

As a consequence of some of the recommendations made at the symposium in Chicago, August, 1973, and outlined in the proceedings entitled, "Dental Biomaterials-Research Priorities," the staff has initiated efforts to begin research into some of the stated areas of need. As noted in the proceedings, more clinical evaluation of the performance of restorative materials is needed: (1) to determine the incidence and modes of failures; (2) to determine the longevity; (3) to validate present laboratory tests and develop new ones so that predictions of success or failure can be made; (4) to determine the effect of composition and manipulative factors on performance; (5) to develop criteria to compare different materials designed for this same purpose. In addition, we are initiating an interagency agreement to answer these questions in regard to clinical evaluation of base alloys for use in fixed prosthodontics, a clinical evaluation of the newer dental amalgam alloys, and an *in vitro* and *in vivo* evaluation of composite resins as posterior restorations.

In the area of pit and fissure sealants, the use of transition metal ions as "mordants" together with newly devised chelating agents seems to be promising as a means of obtaining better adhesion to dentin. It appears that composite materials as sealants and restoratives may eventually be in widespread use, and hence even minor improvements in their composition and performance will have a significant effect on dental health.

Improving the reliability of bonding of pit and fissure sealants and getting definitive answers as to the progression of an incipient caries lesions when covered by sealants may increase its utilization by the

dentists. While preliminary data show that incipient carious lesions are arrested when covered over by sealants, there is a need for definitive data to answer this question to the satisfaction of all concerned.

The Program plans to initiate controlled clinical evaluations of endosseous tooth implants of the best material and design as indicated by the data from the current active grants and contracts as soon as such studies seem appropriate.

The Program also plans to develop clinical evaluations of the most promising materials for maxillofacial prosthetic devices. Meanwhile we will continue to pursue the search for the "best" material and for optimization of currently used materials and techniques.

With the rapid developments in biomedical engineering area, the time appears to be ripe to get both biomedical engineers and dentists together to explore the possibilities of developing better instrumentation in preventive, diagnostic and therapeutic dentistry. We are planning a workshop to be held with consultants from biomedical engineering, orthodontics, and clinical dental investigators to discuss the future course of action.

Poor communication between the scientists who are doing basic research in restorative materials and practicing dentists has been a persistent problem. The Program plans to explore ways to increase dialogue and collaborative efforts between basic and dental scientists. This will be done through a series of meetings, workshops, symposia and sponsored research.

SUMMARY

During FY 1975 the Restorative Materials Program awarded $2.6 million to support 62 research grants and contracts in the areas of filling materials, bonding agents, maxillofacial prostheses, artificial tooth implants and general studies. The support for research on restorative filling materials and implants remained approximately the same as the previous year, whereas funds for research on prevention were increased. In addition, the Program made awards totalling $0.5 million to support 7 training grants, and $77,300 was awarded for 2 individual post-doctoral fellowships and two research career development awards.

Research in restorative filling materials continues to show improvements in composite resins, but these restorative materials are not yet suitable for application in posterior teeth. A rigorous *in vivo* evaluation was done comparing the clinical performance of amalgams, composite resins, and a silicate. This study showed that the composites were superior in marginal adaptation, but the amalgam retained its anatomic form better.

In the area of tooth implantation, preliminary data on bioglass material shows interesting and promising results. Endosseous implants of a cylindrical configuration made of titanium wire have been sufficiently successful in baboons that it may soon be appropriate to reexamine the feasibility of conducting limited clinical investigations of this material in humans. In the near future it may become reasonable to consider other materials, such as the bioglass ceramic and polymethylmethacrylate for potential clinical evaluation.

During FY 1975 the interagency agreement with the National Bureau of Standards continued to produce information on physical/chemical characteristics of tooth structure, basic chemistry and new formulations for bonding agents, such as used for pit and fissure sealants, and instrumentation to measure the wear characteristics in vitro of restorative filling materials. Early studies indicate that two materials, silphenylenes and terpolymers, may prove superior in several respects to the silicones and poly vinyls currently used in maxillofacial prostheses. The new materials score higher in tensile strength, staining characteristics and weatherability.

Partial support was furnished for the Seventh International Symposium on Biomaterials at Clemson University and for the symposium on Interfacial Dynamics of Cutting in Dentistry held in conjunction with the AAS meeting. Program staff also initiated and conducted a meeting to plan a workshop on the relevance of biomedical engineering to dentistry.

Drafted by T. M. Valega and P. F. Parakkal.

ANNUAL REPORT FY 75
SOFT TISSUE STOMATOLOGY AND NUTRITION PROGRAM

INTRODUCTION

The Soft Tissue Stomatology and Nutrition Program was established in April 1975 by incorporating the soft tissue diseases component of the Periodontal and Soft Tissue Diseases Program of NIDR into the Mineralization, Salivary Secretions and Nutrition Program. The new Program thus includes four major components: soft tissue diseases, nutrition, salivary glands and their secretions, and mineralization research. The Program fosters and supports specific research to generate knowledge on a) the cause, treatment and prevention of oral soft tissue diseases and disorders, b) the role of nutrition in the growth, function and health of the craniofacial complex, c) the normal and abnormal salivary glands and their secretions, and d) the mechanism of mineralization.

ADMINISTRATIVE

As of June 30, 1975 the Program consisted of a total of 53 active research grants. Forty of these grants totalling $2.0 million were actually funded during FY 1975. Twenty-five grants ($1.5 million) were awarded for mineralization research, 11 grants ($0.4 million) were made for research on salivary glands and their secretions, and 4 grant were awarded for nutrition research ($0.1 million). Fourteen of the awards were new grants and 7 were competing renewals. The distribution according to the three major subject areas in the Program is shown in Table 1.

Although the total funds awarded for mineralization during FY 75 were essentially the same as the funds awarded in FY 74, it should be pointed out that there has been a change in emphasis of mineralization research towards studies on the biological mechanisms involved in the mineralization process. Thus, it appears that Staff efforts to implement the recommendations of an FY 73 ad hoc advisory committee has been successful in converting the NIDR mineralization research efforts from non-biologic crystallographic research to projects more biological in nature. It should be noted in particular that all 8 of the new grants in mineralization paid during 1975 deal with biological mechanisms of calcification.

Last year a small workshop to identify specific nutrition problems of interest to NIDR was convened and during this fiscal year some of the recommendations of that workshop were implemented. A significant recommendation was that a major effort should be made to expand nutrition research relating to oral health and the training of scientists in this field. Staff efforts to follow this advice has produced gratifying results. During FY 75 NIDR received 10 nutrition research grant proposals and 5 institutional training grant proposals. This represents a 10-fold increase in research grant proposals and a 5-fold increase in training grant proposals when compared to the past two fiscal years.

FY 75 also saw the initiation of 2 research contracts in nutrition totalling $195,000. One of these contracts was awarded to the University of Washington in Seattle, the other to the University of Iowa. The purpose of these contracts is to investigate the role of protein and calorie nutrition on the maintenance of the integrity of oral mucous membranes. The development of these 2 contracts was also helpful in stimulating the additional grant proposals in the area of nutrition mentioned earlier.

To stimulate research on salivary secretions program staff conducted an informal workshop session with participants of the salivary research group of the American Association for Dental Research during its annual meeting in New York City. The main purpose was to identify areas of salivary secretion research which should be pursued during the next few years. As a result of this successful meeting, staff plans to conduct another planning session early in FY 76 which will be followed by a more formal workshop on the role of salivary glands and their secretions in oral health.

In research training, the program expended $399,344 to make awards for six training grants to support 32 trainees. Additionally the program expended approximately $80,000 for the support of six individual fellows. The program continues to support two career awardees at a combined cost of $65,000 and four career development awardees at a cost of $88,000. Of nine recently received and reviewed institutional fellowship award applications, six will train individuals to conduct nutrition research related to oral health, while three will train individuals to conduct research on salivary glands. No fellowship applications were received in the area of mineralization or hard tissue research.

TABLE I ACTIVE GRANTS FY 75

	Active Grants	Funded FY 75	FY 75 Funds (millions)
Nutrition	4	4	$ 0.1
Salivary Secretions	18	11	0.4
Mineralization	31	25	1.5
TOTALS	53	40	$ 2.0

STAFF ACTIVITIES

During the current fiscal year, staff has made visits to institutions for the purpose of monitoring and evaluating ongoing research supported by NIDR as well as for determining the feasibility of initiating research and/or research training in a given area. When indicated, special visits were made in an

effort to program research grant proposals in identified areas of need. For example, specific efforts were made to develop nutrition research because this area has been identified as an area of need. Staff also attended several scientific meetings where both programmatic and monitoring activities were engaged in. These visits and meetings are categorically listed below.

Monitoring, Evaluation and Programming

1. Columbia University, School of Dentistry
   Institute Director and Extramural Program Staff
   visit, Sept. 30, 1974.

2. Meharry Medical College, monitoring and evaluation
   visit, January 13, 1975.

3. Vanderbilt University, programming visit,
   January 14, 1975.

4. Medical College of Georgia, programming
   and monitoring visit, January 15, 1975.

5. Emory University, programming visit,
   January 16, 1975.

6. Georgia Institute of Technology, project
   site visit, January 17, 1975.

7. University of Washington, Center for Research
   and Oral Biology, contract monitoring visit,
   April 22 thru 23, 1975.

8. University of Iowa, contract monitoring visit,
   May 18 thru 20, 1975.

Scientific Meetings

1. Gordon Research Conference on Teeth and Bones,
   Meriden, New Hampshire, July 6 thru 13, 1974.

2. International Trace Mineral Symposium, Wayne
   State University, Detroit, Michigan, July 10
   thru 12, 1974.

3. Gordon Research Conference on Food and
   Nutrition, New London, New Hampshire,
   August 12 thru 16, 1974.

4. Mineralized Tissue Conference, Sun Valley,
   Idaho, July 12 thru 16, 1974.

5. African-American Scholars Workshop on Nutrition in the Sahel, August 24, 1974, Washington, D.C.

6. Mineralization Mechanisms in Invertebrates and Plants Workshop, Georgetown, S.C., October 1 thru 4, 1974.

7. The American Dental Association, Washington, D.C., November 10 thru 14, 1974.

8. Nutrition Study Section Workshop, "Evaluation of Large Scale Nutritional Intervention", January 15, 1975.

9. The American Association for Dental Research, New York City, April 4 thru 8, 1975.

10. Federation of American Societies for Experimental Biology, Atlantic City, N.J., April 15 thru 18, 1975.

11. The American Association of Orthodontics, Las Vegas, Nevada, April 20 thru 21, 1975.

Staff Development

1. Interagency Orientation Step Module, Bethesda, Md., NIH Campus. (Ongoing)

RESEARCH HIGHLIGHTS

Soft Tissue Stomatology

Current research related to oral soft tissue diseases include a variety of virology projects, from basic studies on the complex process of viral assembly to practical clinical tests of antiviral agents. Studies on recurrent aphthous ulcers and dental pulp biochemistry are also reported.

In a basic study at the University of Minnesota, scientists are studying the possibility that viruses may some day be used to incorporate expressible genes into defective cells to achieve normal cellular function. To attain such a goal, scientists must develop an in-depth understanding of viral assembly. Thus, studies are being made of the small bacteriophage Ø 29 as a model intermediate between self assembling simplex viruses and large complex viruses. This particular virus is well suited for such studies because it does not have a superabundance of genetic information.

Scientists at the Center for Oral Health Research at the University of Pennsylvania have detected a viral antigen (CP-1) on the surface of hamster tumor cells transformed by inactivated Herpes simplex virus Type 1. It had

been previously demonstrated that hamsters bearing tumors composed of the HSV-1-transformed cells produce antibodies capable of neutralizing the infectivity of other HSV-1. In the Pennsylvania study the scientists used HSV-1 inactivated by U.V. light to develop an antiserum containing anti-CP-1 antibody. Then, they showed by indirect immunofluorescence that the antiserum reacted specifically with the CP antigen on the surface of the hamster tumor cells. This is the first time that the oral form of the virus inactivated with U.V. has been shown to be part of a tumor system. This study is of particular importance because of the potential link between HSV-1 and the occurrence of oral carcinomas.

In an attempt to develop chemotherapeutic agents to treat viral infections, scientists at the Dental Research Institute of the University of Michigan are investigating chemicals that inactivate virus. One of the antiviral chemicals is Arabinosyladenine (Ara-A). According to the study, Ara-A at low concentrations will suppress lesions caused by Herpes simplex virus in vitro. At higher levels, Ara-A and a similar chemical called Ara-HX completely block replication of Herpes simplex virions. In these studies, the rates of cellular and viral synthesis were measured by pulse labelling virus-infected cultures of synchronized KB cells with tritiated thymidine, a technique which allows cellular and viral DNA to be separated out and studied further. Preliminary findings suggest that the selective antiviral effects involve DNA synthesis.

The results of a retrospective longitudinal study on the prevalence and incidence of recurrent aphthous ulcers (RAU) conducted at the University of Pennsylvania during a 12-year span from 1958 to 1971 was reported recently. This study, involving 503 males and 180 females, showed that RAU prevalence in 1971 (48.3% in males and 57.2% in females) was approximately 12% less than in 1958 when the subjects were younger. A downward trend in severity levels was also noted. According to the authors, the study suggests that the highest level of RAU occurs during the student years because of increased stress during that period.

Pulp Studies

Since bovine dental pulp is rich in collagen and in the enzyme collagenase, investigators at the University of Iowa have used this special oral tissue to study these important proteins. In their work on collagen they have obtained purified extracts of pulp collagen, chromatographically separated them into alpha-1 and alpha-2 chains, and have undertaken analysis of the carbohydrate composition and amino acid sequence of the two chains. In addition, a computer program has been developed to compare amino acid composition of pulp collagen with that of collagen from other tissues. The results indicate that pulp collagen differs from collagens found in chick skin, cartilage and bone. These findings serve as another example of tissue specficity in collagen chemistry.

Nutrition

Studies by scientists at the University of Pennsylvania Center for Oral

Health Research reported last year that Vitamin C deficiency resulted in the formation of hydroxyproline-deficient collagen composed of denatured chains. The denatured molecules are secreted more slowly than hydroxylated molecules and do not form the normal triple helix fibril structure usually formed at body temperatures. In a related study, it was noted that the absence of ascorbic acid in tooth germ organ culture systems causes reversible deterioration of cellular differentiation in addition to the production of hydroxy-proline-deficient collagen.

Meanwhile, a companion study illustrated at the ultrastructural level that the most dramatic dysplasia occurring in Vitamin C deficiency were abnormalities of the dentin and dentin matrices. While initial differentiation of preodontoblasts and preameloblasts proceeded normally, fine structural differentiation into secretory odontoblasts and ameloblasts did not occur. The basal lamina prematurely disappeared, allowing preodontoblasts and preameloblasts to intermingle and form widely scattered islands of hard tissue. Normal levels of Vitamin C resulted in the development of normal ultrastructural components. It was found also that protein synthesis inhibitors produced ultrastructural changes similar to those of Vitamin C deficiency. These findings suggest that Vitamin C deficiency not only disturbs the hydroxylation mechanism, but also may interfere with protein synthesis in general.

Scientists at the University of Minnesota obtained evidence last year that a low fluoride content in the maternal diet caused mouse pups to weigh less at birth and to develop anemia. The anemia was improved by adding fluoride to the diet. Recent experiments have now shown that the addition of fluoride caused the iron or copper content of the newborn mice to increase. The authors believe that fluoride may in some way cause a greater absorption and retention of both copper and iron.

The capacity of oral mucous membranes to serve as a barrier against the invasion of microorganisms or their toxins is important in periodontal disease, aphthous ulcers and other oral diseases. To study the permeability of oral mucous membrane under controlled conditions, investigators at the Massachusetts Institute of Technology have developed an *in vitro* technique employing guinea pig oral mucosa. Using tritiated endotoxin as the penetrating solution, autoradiographs and perfusate analyses were made to determine whether or not the solution passes through the tissue. In tests made so far, it was found that the penetration of the endotoxin was greater in the tissues of animals deficient in Vitamin C than in the tissues of normal animals. In a related study at the University of Washington Center for Research in Oral Biology, scientists have found that the inclusion in the solution of a cationic or anionic surfactant (in low concentration) increases mucosal permeability. This finding is of importance becuase of the prevalence of these substances in tooth paste.

Investigators at the Dental Research Institute at the University of North Carolina have continued their work on the effect of Vitamin D on the maturation of collagen. In earlier reports they had presented evidence to suggest that the normal cross-link pattern in chick bone collagen requires Vitamin D. In

contrast, their studies of skin collagen indicated that Vitamin D has little effect on cross-link formation in this tissue. These findings support the idea that the Vitamin D effect on cross-links is specific for bone collagen.

Investigators at the University of Washington Center for Research in Oral Biology report that their studies of young subhuman primates so far do not demonstrate a significant relationship between the severity of gingivitis and nutritional status. However histologic jaw sections show more alveolar bone resorption and more atrophy of periodontal fibers in malnourished animals than in control animals. Preliminary electron microscopic studies of oral epithelium show a reduction in the width of desmosomes and disorganization of tonofilaments following three to five months of protein calorie deficiency in the infant monkey.

Salivary Secretions

At Temple University, scientists have explored functional and structural changes in the salivary glands of mice after a single injection of isoproterenol. Such treatment causes marked stimulation of DNA synthesis and cell division, especially in the parotid and submaxillary glands. In last year's report the investigators described the stimulating effect of isoproterenol on ribosomal RNA synthesis. At that time it was possible to piece together in sequence the early steps occurring when the parotid glands are stimulated to proliferate. The first step is an immediate increase in synthesis of nonhistone chromosomal proteins which in turn activates the genome resulting eventually in DNA replication and finally mitosis. Further studies necessitate a model system free of cell components which do not react to the isoproterenol stimulation. The homogeneous cell populations required can only be obtained in cell culture systems. Thus, efforts are being made to develop a culture system which will proliferate in response to isoproterenol stimulation.

In experiments using cyclohexamide, an inhibitor of protein synthesis, it was found that stimulation of the synthesis of nonhistone chromosomal proteins ultimately resulted in an increase in chromatin template activity. These experiments provide an independent example of the consequences of nonhistone chromosomal protein stimulation. In another series of investigations these same scientists have investigated the effect of urethane on the prereplicative phase of the isoproterenol stimulated mouse parotid. The results indicate that urethane acts at the level of DNA synthesis itself and has no effect on any of the prereplicative steps of the cell cycle, thus providing a method of dissociating events occurring in the prereplicative phase from the DNA synthesis itself.

In addition to causing alterations in the protein of salivary glands, isoproterenol has also been shown to cause changes in inorganic chemistry of salivary secretions. At the University of Alabama, a grantee has been studying the regulation of electrolyte transport in the duct system of salivary glands affected by isoproterenol. It was reported last year that marked changes in sodium and potassium occur in the duct system of the submaxillary gland under

the influence of the beta adrenergic agent isoproterenol. Prior administration of a blocking agent (propranolol) suppresses the effect of isoproterenol on ductal absorption of sodium. In work just completed it has been shown that calcium in the luminal fluid alters the rate of Na-absorption but not K secretion. Absorption of sodium is enhanced by lowering Ca++ in the luminal fluid. Only small net changes in K secretion occur when calcium is reduced. This is believed to be related to a somewhat enhanced transductal electrical potential. Thus Ca++ in luminal fluid has a regulatory function in Na-absorption. In other studies the use of cytochalasin B to alter ductal cells has provided further evidence that K secretion is mediated by processes at the acinar cell level which are at least partially independent of Na-absorption.

Investigators at the University of Alabama have studied the role of the autonomic nervous system in regulating salivary gland responses. Their results show that parasympathetic nerves induce mitotic bursts in the parotid glands when secretory activity is abruptly increased. The parasympathetic branch also regulates the increase in cell size which accompanies this change in secretory activity. These findings indicate that the autonomic system not only affects gland secretion, but also exerts an influence on growth processes. Other recent findings by this group illustrate a feature of sympathetic influences on gland physiology. When previously fasted rats are fed solid food, the parotid gland empties itself of amylase. This phenomenon appears to require an intact sympathetic innervation since blocking the parasympathetic branch has little effect on the emptying process. The findings described provide evidence that the regulation of normal secretory activities involve both sympathetic and parasympathetic function.

Mineralization

In separate studies, investigators at the University of South Carolina and the University of Colorado are using invertebrate mineralization systems to clarify cellular aspects of the mineralization process. For example, studies at Colorado have demonstrated intracellular nucleating vesicles in the jelly fish statolith. These nucleating vesicles were observed to be membrane-bound and contained an amorphous organic substance. Within the statocyte, the vesicles were observed near the cell nucleus, sometimes in association with the Golgi apparatus. These nucleating vesicles represent the earliest sites discernible in statocytes associated with the initiation of intracellular mineralization.

Studies at the University of South Carolina on larval shell formation in the American oyster show that the cell cytoplasm near the hinge region is stimulated to undergo a series of developments eventually resulting in cell proliferation, calcium accumulation in cells, matrix formation and ultimately shell regeneration. The presence of significant amounts of calcium in the cell suggests that the cell is active in calcium transport associated with mineralization. A special advantage of this system is that it allows investigators to observe accumulation and release of calcium by individual cells.

NIDR grantees at Cornell University have recently conducted research using X-ray radial distribution analysis to determine the atomic arrangement of

amorphous and crystalline calcium phosphates. Their findings indicate that the portion of bone which appears to be amorphous to X-ray diffraction is not the same as synthetic amorphous calcium phosphate.

On other experiments it was discovered that protein-free bone mineral does not cause a pH change in water as a result of chemical conversion of the amorphous phase as typically occurs with synthetic amorphous calcium phosphate. This finding further suggests differences between the amorphous phase of bone and that of the synthetic calcium phosphate.

Recent studies by grantees at the University of Arizona have been successful in further characterizing proteins obtained from fossils as ancient as the Cambrian Period. Their findings suggest that some of these proteins represent well preserved collagen while other degraded fossil proteins appear to be the result of putrefaction of the original animal carcass. To determine whether the collagen-like proteins were indeed derived from the original collagen or from some other origin, these investigators carried out gelatinization experiments in which a comparison was made between the peptide mixtures resulting from water hydrolysis of fresh collagen and a number of fossil proteins having the overall composition of collagen. The findings indicate that the fractions obtained from the gels are the same for both the recent collagen and the fossils, thus supporting the idea that the fossil specimens had been so well preserved that the initial proteins were only slightly altered.

Recent studies at the Institute of Dental Research at the University of Alabama provide firm evidence that calcium and phosphate interactions with various organic components are governed primarily by highly specific stereochemical factors rather than by simple non-specific coulombic forces. In these studies it was found that hydrogen binding is the major factor controlling the binding of phosphate ions to organic components and that effective calcium binding sites are provided by organic components that can compete with water furnishing sets of oxygen atoms in the proper space configuration for combining with calcium. In addition, this work has demonstrated that oxygen atoms involved in binding calcium can be from neutral sites (hydroxyl and carbonyl groups) or from negatively charged sites (carboxyl or phosphate groups). Thus the classical idea that calcium ions bind only to negative sites is invalid. The studies indicate that calcium ions can bind effectively to any site that provides the proper geometrical arrangement of oxygen atoms.

FUTURE PLANS

Nutrition

Future plans for nutrition research involve three specific areas: 1) protein malnutrition, since specific oral manifestations of deficiency are known, 2) hyper- and hypovitaminosis, because they affect the development and maintenance of oro-facial structures, and 3) the potential benefits of sound nutrition, since poor nutrition may compromise the barrier function of oral epithelium. Future efforts will include: 1) continued programming to stimulate a wide variety of proposals on nutrition and oral health, 2) programming for proposals

on the effects of poor nutrition on salivary gland function, on mucous membrane integrity and on tissue metabolism, and 3) continued efforts to expand research manpower, by recruitment from the biomedical manpower pool and by the training of new scientists.

The discovery in guinea pig tissues that calorie, protein and Vitamin C deficiencies cause an increase in the permeability of oral mucous membranes sets the stage for studies in humans to determine whether such deficiencies affect susceptibility to disease. Accordingly, special efforts will be made to encourage such studies.

Soft Tissue Disease

Recent progress in Herpes simplex virus studies suggest that it is now possible to obtain a better understanding of the response of human cells to virus particles and the response of the immune system. Therefore, continued study of the fundamental virology and immunology of Herpes disease will be encouraged. The ultimate goal is to develop a vaccine for the prevention of the infection. However for the present, staff will foster the development of new antiviral therapeutic agents to provide control of the infection until preventive methods are developed. Future activities dealing with soft tissue diseases will also emphasize aphthous ulcers and oral cancer. Special arrangements have been made to collaborate with the National Cancer Institute in dealing with oral cancer research projects. Specifically NIDR staff will encourage studies: a) to determine the cause and cure of oral cancer in existing cancer centers and elsewhere, b) to determine the relationship between Herpes infections and oral cancer, c) to determine the etiology of salivary gland tumors, and d) to develop methods of diagnosing premalignant oral lesions particularly the erythroplasias.

Future plans are to encourage both grant and contract supported research to: a) further characterize the immunologic aspects of Herpes simplex virus infections, b) further characterize animal model systems, and examine factors associated with the tissue localization and reactivation of the virus, c) identify and test antiviral drugs, d) determine the involvement of Herpes simplex virus-1 (HSV-1) in oral cancer, e) develop better means of diagnosing Herpes infections for future epidemiologic studies, f) develop an effective vaccine against Herpes virus.

In the field of recurrent aphthous ulcers (RAU) staff programming will emphasize the following approaches: a) expand clinical and epidemiologic studies of both RAU and Bechet's syndrome to more precisely define the entire syndrome and its spectrum of severity, b) identify the etiologic factors causing the ulcerative condition, c) characterize the immunologic basis of the disease to enhance diagnostic capabilities and to provide insight into possible prevetive measures, d) expand the clinical testing of new treatment agents, e) develop animal model systems, and f) develop interdisciplinary and cross-institutional collaboration.

Salivary Secretions

In view of the increasing evidence that specific salivary components perform specific functions in preserving oral health, staff will attempt to expand research and training activities on salivary glands and their secretions. Specific efforts will be made to: a) characterize the role of salivary glands in oral immunity through studies on salivary IgA, b) encourage studies of salivary proteins and glycoproteins to determine their specific roles in oral disease, and c) expand the capability of using salivary secretions as indicators of health.

Mineralization Research

Fundamental mineralization research is not considered to have high priority with regard to programming research and training. As reported in last year's annual report the mineralization research program was thoroughly evaluated, and since then, plans to change program direction and to cut back support in specific areas have been carried out. The remaining portion of the program is considered to be both stable and vital as an underpinning for NIDR's more disease oriented programs. Program staff plan to continue its careful monitoring of this aspect of the program in order to meet the guidelines of the special evaluation committee on mineralization research.

SUMMARY

The Soft Tissue Stomatology and Nutrition Program includes four major components: soft tissue disease, salivary glands and their secretions, nutrition and mineralization research. Research efforts are designed to expand the knowledge of a) the cause, prevention and cure for oral soft tissue diseases and disorders, b) the role of nutrition in the growth, function and health of the craniofacial complex, c) normal and abnormal structure and function of salivary glands and their secretions, and d) mechanism of the mineralization process.

During FY 75, the program expended approximately $2.0 million for the support of 40 research grants. For research training the program expended $0.68 million for 8 training grants to support trainees and for the support of 9 individual fellows. The program also supported 2 career awardees and 6 career development awardees. Although the bulk of the funding for both research and for research training was awarded to support studies emphasizing hard tissue research, a considerable shift towards the support of nutrition related research and research training was evident.

During the year, staff made visits to eight institutions to monitor and evaluate projects already underway as well as for the purpose of programming new research. In addition, 11 scientific meetings were attended in which

programmatic and monitoring activities were engaged in.

Progress in nutrition research during FY 75 was considerable. In one study it was shown that a deficiency of ascorbic acid causes effects at two different levels. At the molecular level, a deficiency of ascorbic acid results in collagen fibrils deficient in hydroxy-proline which appear as denatured chains rather than the typical triple helical molecular structure. Further observations of ascorbic acid deficiency at the ultrastructural level showed deterioration of cellular differentiation and drastic changes in the morphology of developing scorbutic tooth germs. In an in vitro study, Vitamin C deficiency caused an increase in oral mucous membrane permeability, a deficiency manifestation likely to result in increased susceptibility to local disease. Fluoride deficiency in the maternal diet of mice caused a diminution in the size of pups at birth plus anemia during the newborn period. Restoration of fluoride improved the anemia and also increased the retention of both iron and copper. In related studies, it was demonstrated that Vitamin D was required for cross-link formation in bone collagen but not for cross-links in skin collagen. In primate studies malnourished animals showed more alveolar bone resorption and more atrophy of periodontal fibers than controls.

Studies on isoproterenol-stimulated salivary glands reveal marked stimulation of DNA synthesis and cell division. The first steps involved an immediate increase in nonhistone chromosomal proteins which in turn activate the genome, resulting in DNA replication and ultimately mitosis. Further studies on the effects of isoproterenol on the salivary glands revealed marked changes in the ductal absorption of sodium and potassium. However prior administration of a B-adrenergic blocking agent (propranalol) negates the effect of isoproterenol on the ductal absorption of sodium. Also a lowering of calcium in the luminal fluid enhances sodium absorption but potassium is unaffected. This effect is believed to be related to the enhanced transductal electrical potential. Studies on the pH regulation of saliva via the bicarbonate system reveals that electrical stimulation of the chorda tympani nerve, or interarterial infusion of either acetylcholine or isoproterenol elevates the level of bicarbonate secreted in saliva thus increasing its buffer capacity.

Recent neurophysiological studies on the salivary glands have shown that the parasympathetic branch induces mitotic bursts and an increase in cell size in the parotid glands when secretory activity is abruptly increased. Intact sympathetics appear essential for adequate emptying of amylase from the parotid when fasting animals are given solid food. Such studies confirm the important roles of both parasympathetic and sympathetic innervation in normal function.

Mineralization studies have shown that an intracellular nucleating vesicle initiates the mineralization process in the jelly fish statolith. A study on oyster cell regeneration emphasized calcium transport by the cells. New studies of bone by X-ray diffraction showed that amorphous calcium phosphate in bone is different from synthetic amorphous calcium phosphate. Fossils from the Cambriam Period have been found to contain rather well-preserved collagen and less well-preserved residues of other animal proteins. In a study of the relationship of Herpes simplex virus to tumor production, investigators have

detected a viral antigen on the surface of hamster tumor cells transformed by inactivated Herpes simplex virus Type 1. This is the first time that inactivated oral Herpes virus has been shown to be part of a tumor system. Studies of viral chemotherapy have shown that Arabinosyladenine (Ara-A) and similar chemicals will suppress lesions caused by Herpes simplex virus. In a basic science study of virus assembly, scientists are examining the small bacteriophage Ø 29 to study the possibility that viruses may some day carry expressible genes to defective cells to achieve normal function. In a longitudinal study on the prevalence and incidence of recurrent aphthous ulcers (RAU), subjects were followed over a 12 year period. The results showed that in later years the incidence of this disorder decreased by 12%. It is believed that a high level of RAU occurs during student years because of increased stress during this period. In dental pulp studies, investigators are using bovine dental pulp to analyze the carbohydrate composition and amino acid sequence of the alpha-1 and alpha-2 chains found in collagen. Results indicate that pulp collagen differs from collagen found in chick skin, cartilage and bone. These findings serve as another example of tissue specificity in collagen chemistry.

Drafted by: P. D. Frazier and
M. A. Kinnard

ANNUAL REPORT FY 75

PAIN CONTROL AND BEHAVIORAL STUDIES PROGRAM

INTRODUCTION

Pain and the fear of pain are two of the most powerful forces which prevent people from dealing with their dental problems directly. To increase our understanding of these factors so that their negative influence can be minimized, the Pain Control and Behavioral Studies Program fosters basic and applied research and research training. While the ultimate goal of these efforts is to improve the oral health of the nation, the Program has specific objectives of a more immediate nature. One objective is to support research leading to the alleviation of pain, a powerful and pervasive factor that has special significance in dentistry. The second objective of the Program is to support behavioral research to develop a deeper understanding of how and why people behave as they do in response to dental problems. It is hoped that behavioral science research will lead to more effective control and treatment of these problems.

During the past year, the program achieved progress in meeting its objectives and continued to provide leadership in the areas of oral-facial pain and behavioral research. This report summarizes these activities.

ADMINISTRATIVE

During FY 75, research support provided by the Pain Control and Behavioral Studies Program increased dramatically from 9 projects totalling $404,000 in FY 74 to 19 projects totalling $816,870. Table I on the next page shows the distribution of support by area of research.

In addition, funds for pain research supported through the Dental Research Institutes and Centers Program amounted to $234,000. Four of the eleven new awards were made to young investigators under the NIDR small grants program and the first Research Career Development Award in the field of pain was made to an investigator at the University of North Carolina. In FY 75, the Program supported eleven research training grants, at a level of over $1,000,000, approximately the same level as during FY 74.

The professional staff of the program remained stable during FY 75. Colonel Robert Johnson has served effectively on a one-year appointment as a visiting scientist and will continue until July 1, 1975. On that date he will return to the U. S. Army. It is anticipated that close contact will be maintained with Colonel Johnson in the future and that cooperative efforts with the Department of Defense pain research activities will be developed to a far greater degree than in the past. One area of

research in which these cooperative efforts will be focused is electrical anesthesia, a field of emerging importance. Dr. Edward Driscoll, who served in the Program part-time during FY 75, will increase his Program efforts during FY 76. Dr. Ronald Dubner, Chief of the NIDR intramural pain research program, continued to provide assistance and support to the extramural effort. Dr. Richard Hayes maintained his behavioral studies program activities while serving NIDR in a variety of other assignments, chiefly in the evaluation and analysis of fellowships and NIDR small grant programs.

TABLE I FY 75 DISTRIBUTION OF SUPPORT FOR PAIN RESEARCH

		Number of Grants	Amounts	%
I	Neurophysiology	7	$196,181	24
II	Behavioral Aspects	5	170,397	20
III	Combined Studies (Includes Three Acupuncture Studies)	4	258,498*	32
IV	Clinical	3	191,794	24
	Totals	19	$816,870	100%

*Includes FY 75 funds for one grant which received payment in FY 74.

STAFF ACTIVITIES

Program staff visited 10 universities to discuss potential research endeavors of programmatic interest or to evaluate the progress of ongoing research activities. In addition, staff attended 6 major scientific meetings to present papers and to meet with interested and potential grantees. Support was provided to the Section of Dentistry of the American Association for the Advancement of Science for a symposium on "The Control of Pain" presented at the annual meeting of the Association in New York City in January 1975. This was a follow-up to the successful symposium on pain held at the 1974 AAAS annual meeting. The 1975 symposium was also well attended and served as another effective forum for identifying NIDR as a key factor in national (and international) pain research and for bringing together a wide spectrum of scientists interested in the pain phenomenon. The International Association for the Study of Pain (IASP), formed in 1974 with the active support of NIDR, is planning its first Congress to be held in Florence, Italy, in September 1975. NIDR will support the dental and oral-facial aspects of the scientific program to be presented.

A major workshop in pain was organized by staff and conducted during FY 1975. Work is continuing on the organization of a workshop in the

behavioral sciences. Finally, staff made important progress in FY 75 in working with the American Dental Association, American Association a pain control center for research and education in several dental schools. Detailed descriptions of the workshops and the cooperative efforts to establish pain control centers are presented in other sections of this report.

RESEARCH HIGHLIGHTS

1. Myofascial Pain-Dysfunction Syndrome (MPD)

Patients with the MPD syndrome experience varying degrees of pain and discomfort associated with the temporomandibular joint. At the University of Illinois a major study supported by NIDR has been investigating the role of psychological and physiological factors in the etiology and treatment of this syndrome. The study includes four major areas of investigation: placebo effectiveness, time-limited psychotherapy, response specificity, and a long-term evaluation of conservative therapy. Findings from these investigations are discussed in the paragraphs to follow.

Because past research has demonstrated that one of the peculiar psychological characteristics of MPD patients is their marked response to placebos, and since occlusal equilibration is one of the most popular treatment modalities, a placebo equilibration study was done in 25 MPD patients to see what part of the therapeutic effect of occlusal equilibration could be attributed to psychological factors. A gnathological analysis of occlusion was done, the patients were shown their own occlusal disharmonies, and they were told the positive benefits of treatment. A mock equilibration was then performed that consisted of light grinding on non-occluding surfaces of the posterior teeth. Symptoms were determined initially and at 1-2 week intervals after each of two treatment sessions. Of the 25 patients treated in this manner, 16 (64%) were dismissed with complete or major improvement in symptoms. These findings confirm previous positive results with placebo therapy in MPD patients and strongly support a non-occlusal concept of etiology.

A second study at Illinois evaluated the effectiveness of time-limited individual psychotherapy in MPD patients. Of the 23 patients who completed the 12 weekly sessions, 15 (65%) showed complete remission of symptoms. Since most MPD patients do not admit readily to having emotional problems, and because the majority respond to other forms of treatment, psychotherapy is not suggested as a primary modality for patient management. However, when patients fail to respond to conventional methods, short term therapy appears to offer a reasonable alternative.

In the third project at Illinois, scientists studied the tendency of psychophysiological disorders to localize in particular areas of the

body. By monitoring skeletal muscle activity (masseter, frontalis and gastrocnemius), heart rate and galvanic skin resistance in MPD patients and normal individuals subjected to physical and psychological stress, the investigators demonstrated that MPD patients' greatest response was in the masseter muscle activity while that of the controls was in heart rate. This demonstration of elevated masseter activity in response to stress indicates that the muscles of mastication are target areas for MPD patients. Such findings support the concept that MPD syndrome is a psychophysiologic disorder.

In the fourth Illinois study, investigators evaluated conservative treatment in MPD treatment because of the strong indications that this syndrome is essentially a reversible, functional disorder. Conservative treatment includes mild drug administration, psychotherapy, and placebo tooth grinding, but specifically excludes surgery, local injections, strong systemic drugs, and extensive tooth grinding. To determine the long-term effects of such management, 100 patients who had been previously treated successfully were re-evaluated. Ninety-four percent were still feeling and functioning well as long as 8 years after treatment, thus confirming the efficacy of the conservative approach to MPD therapy.

2. Acupuncture Studies

Because of the wide public interest in acupuncture and its potential usefulness in treatment of dental and other pain conditions, NIDR is supporting a major acupuncture research project at the Massachusetts General Hospital in Boston, Massachusetts. In this study, acupuncture is being evaluated, not only as a treatment for pain, but also as an experimental tool to enable scientists to study the basic aspects of the pain phenomenon.

Four studies of the effects of acupuncture on ischemic pain induced experimentally have been completed at Massachusetts General Hospital. The various studies involved 73 subjects and 369 experimental trials. The evidence indicates clearly that acupuncture procedures exert a strong placebo effect. Investigators must now determine whether the technique also achieves supra-placebo efficacy (physiologic pain relief over and above that due to psychologic suggestion).

In one project a systematic study was made of the different operator variables encountered in the practice of acupuncture and attempts were made to relate these variables to differences in rates of success. In the experiment, each of eight experienced acupuncturists used procedures of his/her choice to control progressively increasing ischemic pain induced experimentally in 12 healthy male volunteers. Pain tolerance was measured both under acupuncture and a no-treatment condition. The results demonstrated that: (1) each of the eight acupuncturists did prolong pain tolerance beyond that of the no-treatment condition; (2) the acupuncture effect was more definite for moderately distressing pain than for higher levels; and (3) differences in success rates among acupuncturists were sufficiently

clear-cut to permit selection of promising procedures for later controlled experimental study.

Also, in progress is an extremely interesting study of the relationship between the ability of individuals to be hypnotized and their response to acupuncture analgesia. When completed these experiments should shed light on the currently controversial issue as to whether or not acupuncture is simply another form of hypnosis.

To control pain during the preparation of teeth for restorations, investigators at the Medical College of Georgia are studying ways to apply local anesthetics to the dental pulp through the dentin. In in vitro studies they have examined the permeability characteristics of the natural dentin and have also tested iontophoresis as a means of increasing the permeation thru dentin of the local anesthetic, lidocaine. Through iontophoresis employing a current of 1 milliampere per minute the investigators have been able to increase the the rate of lidocaine permeation through dentin by 400%. Thus, the method holds promise for achieving highly localized pulp anesthesia.

WORKSHOPS CONDUCTED

NIDR convened a workshop on oral-facial pain in Bethesda, Maryland, in November 1974. This workshop identified information necessary for the proper diagnosis and treatment of vascular, neurologic, musculoskeletal, and psychologic pain originating in the oral-facial region. At the meeting a preliminary classification and standard terminology for the diagnosis and treatment of oral-facial pain were developed, a standardized data collection and retrieval system for clinical information on oral-facial pain was discussed, and the initial development of a suitable system was begun. Publication of the major conclusions is planned.

On February 15-16, 1975, the first session of a two-stage workshop on Psychological Problems Relating to Dentistry was held in Boulder, Colorado. Participants included behavioral scientists with varying degrees of previous involvement with dental problems. During the excellent interchange of ideas and knowledge, it became apparent that: (1) the dental field offers many opportunities to psychologists to develop and test basic psychological concepts and techniques, (2) dentistry can benefit greatly from the contributions of the psychology community, (3) there is a need for greater dissemination of knowledge of dental psychological problems to the psychology research community, and (4) in the present state of research development a workshop could not recommend specific areas for emphasis other than those which were already obvious to NIDR. Three members of the workshop met with staff in New York on April 10, 1975, to develop the plans for the second stage which is scheduled for the winter of 1975.

PAIN CONTROL EDUCATION AND RESEARCH CENTERS

During FY 74, staff initiated discussions with the American Dental Association concerning the establishment of centers in dental schools for research, research training and related educational activities in oral-facial pain control. These efforts resulted in a proposal to be submitted to various foundations for funding through the American Fund for Dental Health. However, because of the depressed national economic climate and other factors, funding for this project has not yet been realized. Nevertheless, when staff presented a progress report and the current status of this cooperative project to the Council of Dental Research of the American Dental Association at its annual meeting in May 1975, the Council again expressed its vigorous support for this effort. At present, plans are underway for another meeting of representatives of the American Dental Association, the American Association of Dental Schools (whose support for the program has been strongly affirmed by its Executive Director) and the National Institute of Dental Research to consider all funding possibilities and the best strategies for their implementation.

FUTURE PLANS

Emphasis will continue to be placed on developing meritorious pain and behavioral research relevant to dentistry. Vigorous programming efforts will be undertaken to alert researchers to the opportunities for investigations in areas relevant to oral-facial problems. In the pain area, particular efforts will be made to develop projects in ambulatory anesthesia, intravenous sedation, drug interactions and electrical analgesia and anesthesia. In the behavioral area, all aspects of the psychosocial implications of dental diseases and oral-facial problems need exploration because of their relative state of underdevelopment. Specific efforts will also be made to develop a small number of multidisciplinary oral-facial pain research centers to integrate the basic and clinical pain and behavioral research. As the possibilities of research training through institutional and individual grants increase, special efforts will be made to develop manpower resources. Efforts to strengthen the educational aspects of pain control in dental schools will include implementation of the cooperative program for pain centers described above and a renewed attempt to establish a pain control academic award similar to the highly successful Pulmonary Academic Award of the National Heart and Lung Institute.

SUMMARY

The Pain Control and Behavioral Sciences Program markedly increased its support of pain and behavioral research during FY 75. It continued also to provide key leadership and a unique Federal focus for pain

research in general. This report highlights significant research progress in the etiology and therapy of temporomandibular joint problems and cites initial efforts to understand how acupuncture works in pain relief. One of these studies demonstrated that stress in MPD patients caused increased masseter muscle activity, a finding which suggests that the muscles of mastication are target tissues for stress in these patients. Some of the difficulties associated with the classification, diagnosis and treatment of oral-facial pain disorders have been identified and clarified in a major workshop that laid the foundation for further advances in this important area. Progress was also made in strengthening the teaching programs on pain control in dental schools. Behavioral research related to dentistry was advanced both by providing increased grant support and by clarifying key issues in a workshop setting. It is anticipated that progress will continue to accelerate during FY 76 in all of the important areas mentioned in this report.

Drafted by A. Ganz

ANNUAL REPORT FY 75

DENTAL RESEARCH INSTITUTES AND CENTERS PROGRAM

The Dental Research Institutes and Centers Program was initiated in 1967 as an experimental support mechanism to provide additional stimulus to dental research, because the scientific base of dentistry was developing too slowly through conventional grant mechanisms. Thus, steps were taken to concentrate the resources and efforts of a few universities to establish environments which would attract high quality scientists from many different fields to work as interdisciplinary teams on dental problems. It was anticipated that these scientists would interact with existing dental investigators and clinicians, as well as with members of traditional basic science departments to derive the greatest possible benefit from existing dental research capability and other institutional research strengths.

This new approach to oral health research is intended to enlist the collaboration of all appropriate elements of the University. It is recognized that its ultimate success depends upon the leadership of the director with the active support of the university administration, the scientific excellence of the research staff, the establishment and maintenance of a suitable environment, continuing program evaluation, with modification as indicated, and reasonably stable financial support.

The institutes and centers are a vital part of the NIDR Extramural Programs. Since their research contributes to the objectives of the six categorical program areas and complements research supported by other mechanisms, highlights of their research are not included there. Instead, they are presented in the categorical program reports to provide a more complete picture of the total research efforts in each area. Thus, the present report deals only with administrative and policy matters pertaining to institutes and centers.

The five institutes and centers at the Universities of Alabama, Michigan, North Carolina, Pennsylvania and Washington are completing their eighth year of support. Within these institutes and centers, 150 principal investigators are conducting approximately 180 projects in collaboration with many other investigators from basic science and clinical departments of the parent universities. These collaborative efforts also involve scientists from over 90 other institutions in the United States and in 13 other countries. In addition, approximately 200 students and postdoctorals are receiving research experience under the guidance of institute/center investigators.

The research of the five institutes and centers covers a broad spectrum of problems relevant to the improvement of oral health. It ranges

from fundamental problems, such as the role of immunological mechanisms in periodontal disease or the nature of the connective tissue destruction in periodontal disease, to clinical field trials of caries-preventing agents and new treatment measures for repair of cleft lips and palates. This past year the research output was approximately 500 scientific papers. These research programs are becoming well-established, and several of the investigators have received national and international recognition for their contributions to science.

In FY 74 the institutes and centers were faced with a financial crisis when their total budget was reduced to $5.85 million. However, the NIDR was able to transfer an additional $1.3 million from other sources so that the institutes and centers could continue to operate that year without sacrificing essential personnel. Subsequently, the budget for FY 75 was increased to $7.4 million, which is equivalent to the final FY 74 level. In addition, the institute/center investigators have been successful in partially defraying inflationary costs through independent grants and other sources of support. Nevertheless, it has been necessary to curtail equipment purchases for the last three years. During this period projects have been slowed while scientists waited to use over-burdened equipment, and other projects have been postponed for lack of equipment. Furthermore, some of the existing equipment has become worn and needs replacement. It is hoped that funds can be provided for equipment purchases in the near future.

The five-year renewal application for the Center for Research in Oral Biology at the University of Washington was approved this year, with the new project period to begin on June 1, 1975. The Universities of Michigan and North Carolina are preparing their renewal applications for submission next fall. Meanwhile the Universities of Alabama and Pennsylvania will be extended with funds for one year each to stagger renewal dates so that the review workload will be spread more evenly. After a two-year search, the University of North Carolina appointed a new Director, Dr. Philip F. Hirsch, whose term began on May 1, 1975. Michigan is currently seeking a new Director.

NIDR continues to encourage interaction and collaboration between institute/center investigators and other scientists. The most recent such endeavor was a two-day scientific meeting held at NIDR. The meeting was planned by a group of NIDR staff representing the Intramural Programs, Extramural Programs and the Director's Office. The general topic of the meeting was research related to craniofacial anomalies. Scientists from each of the institutes/centers and from NIDR's Intramural Program presented their work related to craniofacial anomalies for discussion by the group. Lively discussions resulted in an excellent exchange of information. Participants enthusiastically endorsed this type of meeting and recommended that additional meetings organized with different topics and participants be held in the future.

The FY 74 Annual Report of this program included a description of efforts to develop a method for the evaluation of the dental research institutes and centers. That report referred to a nearly completed outline for evaluation which was to be critically reviewed by a group of consultants and eventually finalized. However, when the consultants reviewed the plan, they concluded that the project was unrealistic and would be too expensive to undertake. In further staff discussions, the scope and focus of the project were narrowed and an attempt was made to write a request for contract proposals to conduct the evaluation. However, this approach also appeared to be unsuitable because of persistent methodological problems. As a result, staff sought advice from another consultant who had had experience with the center mechanism of support. In the meantime, the formal evaluation of the NIDR's periodontal diseases research programs had been initiated and was well underway. Furthermore, similar evaluation projects are planned for all of the other categorical program areas. Since these projects will include evaluation of all of the research going on in the institutes and centers, the need for a separate study to evaluate the institutes and centers seemed to be diminished. Consequently, the decision was made to await the findings of the categorical program evaluations before taking further action.

Drafted by E. Rigg

PART IV

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

INTRAMURAL RESEARCH

July 1, 1974 - June 30, 1975

Compiled By

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Preface

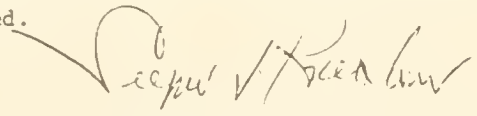
Progress in scientific research is often so subtle that it escapes notice--and the achievements of those individuals who support that research are even less obvious. Only when dramatic discoveries are announced do the contributors to that effort gain some bit of recognition. Still, on a day-to-day basis many dedicated people are working diligently toward that eventual break-through. The annual report at NIH provides each participant in the organizational research effort with an opportunity to reflect on, evaluate, and document their contribution to science on an annual basis. This NIDR Annual Report is a record of our Institutes' activities and progress during fiscal year 1975.

For convenience in compilation and distribution, the Report is prepared in five volumes: Part I, Office of the Director and Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Collaborative Research Projects. This is the fourth year that we have combined the individual project report with the SSIE Notice of Research Project form (PHS 166) and find it most effective for our needs. These are printed on blue paper as a separate section of Volume I.

The numbering system has been changed slightly this year to conform with the NIH-wide practice for numbering grants and contracts. All intramural research projects will bear the same number during their life time and will have a "Z01" prefix. The two digits immediately following the five-digit number indicate the number of years that the project, or some identifiable portion of that project, has been active.

It should be pointed out that while the NIDR Annual Report is not a restricted document, it was prepared for administrative use at NIH and not for public distribution. No attempt has been made to evaluate the quality of research--this has been done by study sections, advisory groups or laboratory and branch chiefs--and the comments of the various contributors to this document are their own.

Recipients of this Report are encouraged to familiarize themselves with the Contents and Indexes and constructive criticism aimed at its overall improvement will be welcomed.



Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

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PART V - COLLABORATIVE RESEARCH PROJECTS

Report of the Acting Director of Intramural Research

National Institute of Dental Research

September 15, 1974 to June 30, 1975

The Acting Director of Intramural Research took up his assignment September 15, 1974 and his activities have been mainly those of administration. Considerable time and effort has been required to develop a knowledge of modes of operation of NIH Intramural programs, and in becoming acquainted with NIDR Intramural personnel and with the Scientific Directors of other Institutes.

A few items outside of strict administrative work which have resulted from the initiative of the Acting Scientific Director can be cited:

(1) As a way of promoting communication between workers in the several of the NIDR Laboratory/Branches about the research in the other Intramural units a series of Staff Seminars has been developed. At two week intervals a member of a Lab/Branch presents for discussion one phase of the research work in his Lab/Branch. These presentations almost always engender useful discussion. It is hoped that in this, and other ways, all NIDR workers will gain a better knowledge of the work of the Intramural Program as a whole than has appeared to be the case in the past.

(2) A mechanism of thorough review of the work of the Lab/Branches has been initiated which is supplementary to that performed by the Board of Scientific Counselors and may, in fact, be more effective than that of supplied by the Board. The plan, which is actually a revival of a plan formerly used and now employed to some extent in review of Intramural activities of other Institutes, involves the formation of a committee composed of those Scientific Counselors who have special knowledge and expertise in the area of work of the Lab/Branch which is being reviewed, with the addition of ad hoc members drawn from other Institutes and from the academic sphere, the latter being chosen solely for their special knowledge.

To date two Laboratories have had their work reviewed in the manner in FY'75. These are: Laboratory of Developmental Biology and Anomalies and Laboratory of Microbiology & Immunology. The formats of each review

were very similar. The workers in the Laboratory made 10-15 minute descriptions of their work which were followed by discussion. At other sessions the committees discussed with the Laboratory Chief the rationale of the work in his unit and the plans for further development of the research.

The Committees provide the Scientific Director with a written detailed evaluation of each segment of the research of the Laboratory being evaluated.

(3) At the instigation of the Acting Scientific Director a contract with the Brookhaven National Laboratory is about to become effective with a probable starting date of July 1, 1975 to develop a new method for determination of fluoride. This method depends upon proton activation and hence requires no chemical manipulation of the sample.

(4) Activities in the way of discussions and plans are now going on which give promise of arranging for analyses for fluoride in the "market-basket" food collections made by the U.S. Food and Drug Administration. These analyses, when they are completed, will correct a serious gap in our knowledge of the fluoride intake of humans from food.

(5) A very considerable amount of time has been spent in editing the English translation of a book published in Russian by R.D. Gabovich and G.D. Ovrutskiy with the title "Fluorine in Stomatology and Hygiene." The translation in many places is less than perfect, particularly with respect to names and literature citations. This book will be a useful source of information from Russian sources which is not otherwise analyzed.

REPORT OF THE SYSTEMATICS UNIT

NATIONAL INSTITUTE OF DENTAL RESEARCH

In September 1974 the Microbial Systematics Unit was established in rented quarters at the American Type Culture Collection (ATCC) to collaborate in establishing a National Microbiological Data Center. This location was chosen because the ATCC is the repository for the largest number of type strains of microorganisms in the world.

At present there are tens of thousands of scientists, physicians, public health personnel, and others involved in some aspect of microbiology in the United States. The number of microbial strains isolated, characterized, and in (many cases) preserved, by individuals runs into the millions. Hundreds of millions of bits of information have been developed on these strains. However, these data are not resident in a single, centrally located system, permitting rapid and efficient utilization. Because of the large volume of information involved and because, in several applications, such as classification and identification, mathematical manipulations of the data are required, electronic processing of these data is necessary.

In collaboration with personnel of the Microbiology Department, University of Maryland; the ATCC; the Food and Drug Administration (under a contract to the ATCC), microbial strain data are being entered into the data bank with the objective of generating a system for providing such services as: data on specific organisms and/or groups of organisms, a locator service for strains with special characteristics, identification of unknown isolates, cluster analysis definition of parameters of taxa, data management and report writing aids for research purposes, aids in quality control of tests, methods, and laboratories, and communication of data via common format.

Much of the data already entered are descriptive of oral bacteria and related types. The information about these strains includes the source of isolation, pathogencity, morphology, physiology, nutrition, antibiotic sensitivities, metabolic reactions, serotypes, etc. For searching, report writing, statistical analysis, etc. any of these kinds of information can be combined. A pilot data management program has been written and tested. It is usable by the working microbiologist after a few hours of

instruction and practice. It requires no prior knowledge of computer technology. The data management program is used to restructure the data so that they are directly compatible with the input requirements of any other analytical program.

Future progress will allow numerical taxonomy studies of the microbiota of the oral cavity to clarify the classification of the varied biotypes in this ecological system. Such clarification is required for epidemiological studies of transmission of oral disease of microbial etiology. A long term goal is the building of probalistic systems for computer-assisted identification of oral microbiota.

Summary Report of the Laboratory of Developmental Biology & Anomalies
National Institute of Dental Research

The staff of the recently created Laboratory of Developmental Biology & Anomalies is now collected together on the fourth floor of Building 30 in three sections, Craniofacial Anomalies Section, Connective Tissue Section and the Genetics and Epidemiology Section. Dr. J. D. Niswander, Chief of the Genetics and Epidemiology Section, is currently undertaking clinical training at the University of Maryland Dental School.

Teratology and Development of Oral-Facial Structures

It has been found that a variety of teratogenic agents produce oral-facial malformations, especially of the secondary palate and mandible by altering inhibiting molecular or morphological events. It has been only in the past year that malformations of the primary palate, resembling certain human birth defects such as the Treacher Collins syndrome (mandibulofacial dysostosis), have been attained in the experimental animal by altering the normal formation, migration or differentiation of neural crest cells. Among those teratogens are vitamin A, x-irradiation and cadmium.

It has also been recently observed that the spontaneous incidence of cleft lip in the Ajax strain of mice can be altered or suppressed by single or repeated exposure to x-ray and can be induced in the rabbit by treatment with cyclophosphamide (a radiomimetic drug) at critical stages of development. In the Ajax mouse apparently these agents alter the shape and "mass" of oral-facial structure and allow an otherwise inadequate number of mesenchymal cells to form the primary palate.

New information has been obtained on the key steps in secondary palate formation. During the development of most animals, the palatal shelves grow down from the maxilla and lie alongside of the tongue. Rather abruptly and late in development these shelves attain a horizontal position above the tongue, apposing shelves adhere and then fuse. These events can also be achieved by in vitro preparations of the tissues. Therefore the developing palate is particularly suitable for study.

Now it has been found that the shelves obtained from fetuses 40-48 hours prior to elevation and fusion can be induced to develop prematurely by exogenous cyclic adenosine monophosphate (cAMP). This compound causes certain epithelial cells in the palate to cease DNA synthesis and induces their subsequent death. Addition of epidermal growth factor (EGF) prevents the programmed cell death of medial edge cells. This action of EGF is reversed by cAMP. The so-called "programmed death of cells" is encountered in the development of many tissues and could be mediated by cAMP. The distribution of specific receptor proteins could explain the responsiveness of different cells.

A variety of teratogens have been used to probe developmental systems. These substances include diazo-oxo-norleucine which has now been shown to inhibit palatal adhesion by blocking the synthesis of surface glycoproteins. Chlorocyclizine has been shown to induce abnormalities in the palate by accelerating the degradation of proteoglycan and hyaluronate.

Dilantin is thought to be causally related to the increased occurrence in cleft lip observed in the children of epileptic mothers. Recently we have been able to produce cleft lip in certain strains of mice with dilantin. Reduced dietary calcium and vitamin D increase the incidence of defects with dilantin.

Mechanism of Chemotaxis - Recent studies from this laboratory have established that leucocytes are attracted to N-formyl methionine and peptide derivatives of N-formyl methionine. It is possible that such peptides are produced by bacterial but not animal cells and represent unique chemical signals to which leucocytes respond. Evidence is accumulating to indicate that cleaveage of these peptides is an essential part of chemotaxis. This suggest that the leucocytes possess both a receptor and a related protease. Considerable potential exists for the practical use of these peptides. They appear to be active *in vitro* in the presence of tumor extracts which block chemotaxis to complement derived factors.

Connective Tissue Studies

We are undertaking an in depth study of the formation and remodeling of connective tissues. Previous studies have established that collagen is synthesized in precursor form (procollagen). Now we have isolated types I, II and III procollagen and have prepared antisera against these proteins. Professor Charles Leblond, currently a Visiting Scientist, in the Laboratory of Biological Structure, NIDR, is using these antibodies to identify the cells synthesizing these proteins. Interesting results have been obtained on the developing dentition and it is hoped such studies will be extended to other developing tissues.

Basement membrane contains a collagenous component, type IV collagen which is as yet poorly characterized. In studying the matrix produced by a murine chondrosarcoma, we have found that the tumor produces basement membrane not cartilage. The collagenous protein has been isolated and partly characterized. Interesting differences from other collagens in size and reactivity have been found. It is hoped that continued studies will clarify the components and molecular structure of basement membrane.

Regulation of Connective Tissue Synthesis - Considerable effort is now applied to the preparation and characterization of mRNA coding for procollagen chains. Here, the first step was to prepare mRNA from tissues synthesizing collagen and demonstrate that it could be

translated in vitro into collagenous proteins. This part of the work has been achieved. More recently, we have attempted to identify the mRNA for types I and II procollagen chains. Here we are using tissues both embryonic and tumor where the synthesis of a single type of collagen is a major cellular activity. In addition, we are using specific antibodies against procollagen to isolate polysomes active in their synthesis. It is hoped that specific nucleic acid probes such as cDNA can be synthesized, using the isolated mRNA as a template, to allow us to measure the number of genes and the amount of mRNA in developing tissues.

Molecular Basis of Genetic Disorders - Studies have been carried out on inherited defects affecting connective tissues. The alterations in the tissues of most patients with the Ehlers-Danlos syndrome are the result of defects in the crosslinking of type I collagen. The specific defects include hydroxylysine deficient collagen (type VI EDS), failure to convert procollagen to collagen (type VII EDS) and lysyl oxidase deficiency (type V EDS). Now we have found that patients with a severe form of the Ehlers-Danlos syndrome (EDS IV) have a quite different defect. The tissues of these patients lack type III collagen and cells from these patients do not synthesize this protein. Type III collagen is a major constituent of skin, aorta and intestine and its absence accounts for the fragility of these tissues in EDS IV patients.

Studies on brachymorphic mice which have a recessively inherited defect of cartilage, have established that the proteoglycans in cartilage are undersulfated.

Epidemiological Studies

We have tried to document the existance of a major maternal effect in human cleft lip and palate. Over 10,000 pedigrees have been examined and no evidence for a major persistant maternal effect has been found. Such findings supported our previous finding that no persistent abberation in thyroid metabolisim was found in mothers with cleft lip children. We provided evidence that dilantin and/or maternal epilepsy may account for a small percentage of cleft lip with or without cleft palate in the human population.

The most advanced methodologies in segregaton analysis have failed to discriminate between a two-allele single locus hypothesis or the multifactional model for the inheritance of human cleft lip or isolated cleft palate. We have accumulated data ascertained by the adult proband method. Analysis of this data shows that the multifactional method has better fit to the data than the single locus model.

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Summary Report
Laboratory of Biochemistry

Late in the last fiscal year and early in the present fiscal year, the Laboratory of Biochemistry lost the Connective Tissue Section, which became the nucleus of the Laboratory of Developmental Biology and Anomalies, and the Cell Biology Section, which was disbanded with some of its major investigators transferring to the National Cancer Institute. Two Sections, the Protein Chemistry Section and the Enzyme Chemistry Section remain. The Laboratory gained newly refurbished laboratories and offices on the first floor, space on the second floor adjacent to the Laboratory of Biological Structure, and access to electron microscope and other facilities in that Laboratory.

In association with these geographical and administrative changes, extensive changes in the personnel of the laboratory, particularly at the postdoctoral fellow level, have occurred. Two NIH Fellows and a Visiting Fellow have joined the Enzyme Chemistry Section to work with its two senior investigators. One senior scientist (a biophysicist) and and a Senior Staff Fellow (a biochemist with extensive experience in proteoglycan biochemistry) joined the Protein Chemistry Section to expand its program. At the postdoctoral fellow level, the departure or transfer of several persons left one who has been joined by four recently arrived fellows. Positions have been committed for an additional four who will arrive in the next few months. The Laboratory programs continue to be supported by a competent and dedicated group of chemists, biologists and secretaries.

The program of the Enzyme Chemistry Section is essentially unaltered with its studies centering around the enzyme transglutaminase which introduces isopeptide crosslinks into proteins. The number of transglutaminases and the structures into which they introduce crosslinks continues to expand showing the major biological role of this method of stabilization. In addition to the well known example of fibrin clots, it has been shown that certain hair and epidermal proteins, senimal plasma proteins and perhaps cell membranes and myofibrils are crosslinked by transglutaminase.

The program of the Protein Chemistry Section still includes active studies on collagen chemistry including the characterization of Ascaris cuticle collagen, the development of improved methods to prepare monomeric, unaltered collagen, and the nature of the C-terminal nonhelical region which is important in crosslink formation and perhaps in noncovalent interactions that regulate fibril firmation. Collaboration with investigators in the Laboratory of Developmental Biology and Anomalies continues in areas of common interest.

Increased emphasis is being placed on relating the primary structure of collagen to higher levels of structure. The elucidation of the details of how collagen molecules are packed in collagen fibrils and the regulation of fibril formation are major goals. This is being approached using computer studies of the amino acid sequence to predict molecular interactions, biophysical methods with emphasis presently on nuclear magnetic

resonance, electron microscopy, and artificial crosslinking studies to try to locate points on collagen molecules that are close to each other in the fibril. In many of these studies collaboration is being maintained with programs in the Laboratory of Biological Structure which have common features in either methods or experimental questions.

A completely new program started near the end of the year is the study of the structure, chemistry and biosynthesis of proteoglycans. Recent advances in this important area of research make it possible to do definitive studies at the molecular level and, as in the case of collagen, relate them to higher level structure. Since proteoglycans are major constituents of cartilage and other connective tissues this is an important breakthrough. It should eventually make possible a better understanding of interactions between proteoglycans and collagen which together are responsible for the structure of cartilage and other connective tissues and are intimately involved in complex developmental processes.

Having completed a rather extensive reorganization, we look forward to a highly productive period in an area of fundamental importance to oral disease.

Summary Report of the Enzyme Chemistry Section
Laboratory of Biochemistry
National Institute of Dental Research

Background

Studies carried out over the past several years have been directed toward characterization of enzymes, termed transglutaminases, that are responsible for the formation of γ-glutamyl amide bonds in proteins and polypeptides. These enzymes catalyze transfer reactions at the carboxamide group of peptide-bound L-glutamine with a high degree of stereospecificity (for review see (1)). In the presence of acceptor amines, the transfer reaction results in the formation of substituted amides ($-CONH_2 + RNH_2 \rightarrow -CONHR + NH_3$).

One of the well-characterized covalent cross-links between and within protein molecules is the ε-(γ-glutamyl)lysine bond. There has been increasing evidence for the presence of this cross-link in fibrin clots, cell membrane, glycerinated myofibrils of muscle, proteins of seminal plasma, native wool keratin, and the citrulline-containing protein fraction of hair (for review see (1)). The wide occurrence and obvious importance of γ-glutamyl amide bonds has led us to focus attention on the enzymes responsible for their formation.

Progress

The transglutaminases isolated from red blood cells have been studied kinetically and immunochemically. The enzymes from human and guinea pig erythrocytes display identical kinetic properties which are also identical to those of the guinea pig tissue enzyme. These red blood cell enzymes cross-link fibrin by means of ε-(γ-glytamyl)lysine bonds and catalyze formation of a single ε-(γ-glutamyl)lysine bond in the hemoglobin molecule. The human red blood cell enzyme shows cross-reactivity with rabbit antiserum to the guinea pig liver enzyme (2).

A number of molecular properties of human plasma protransglutaminase (blood coagulation factor XIII) and of the active enzyme (factor XIIIa) formed by thrombin activation have been determined. Several properties of the protransglutaminase from blood platelets have also been investigated. These include: a) The disulfide - sulfhydryl distribution in the subunits of the plasma zymogen. The catalytic subunits (a chains) contain 12 -SH groups per molecule and no disulfide bonds. The noncatalytic subunits (b chains) have no -SH groups, but contain 32 to 34 disulfide bonds per molecule (3,4); b) The subunits of the plasma zymogen have been separated. The noncatalytic subunits may be combined with platelet zymogen to form a zymogen indistinguishable from that of the plasma; c) An active site group of the plasma and platelet enzymes has been identified as an -SH. The stoichiometry of inactivation of the enzymes by [^{14}C]iodoacetamide and by 3-nitro-4-hydroxy-α-bromoacetophenone shows that total loss in enzymatic activity is accompanied by incorporation of one mole of inactivator per molecule of enzyme. These findings suggest that both enzymes catalyze their reactions by a so-called "half-of-the-site" reaction requiring participation of a subunit structure for catalytic activity (3,4); d) The plasma zymogen is

not dissociated by Ca^{2+} and remains as a tetramer structure containing 2 a chains and 2 b chains. Upon activation by thrombin in the absence of Ca^{2+}, the enzyme is found also to be a tetramer containing 2 b and 2 modified a chains. However, when Ca^{2+} is added to the active enzyme it dissociates into a chain dimers and b chain dimers (3). The dissociation constant for Ca^{2+} estimated from the requirements for this dissociation (1 to 2mM) is close to that determined from Ca^{2+} in its function as an activator for the amine incorporation reaction (5). This suggest that it is the a chain dimer, dissociated from b chains, that is catalytically active; e) The subunits of thrombin-activated plasma transglutaminase have been separated by gel filtration in the presence of Ca^{2+}. Removal of Ca^{2+} has been shown to result in reassociation of the subunits to form a tetramer indistinguishable from that found in the absence of Ca^{2+}; f) The zymogen from platelets (a2) is activated by thrombin at a significantly faster rate than that from plasma (a2b2). A proenzyme prepared by combining the isolated b chain dimer from plasma enzyme with platelet zymogen was found to be activated by thrombin at the same rate as the plasma zymogen. This is substantial evidence that protransglutaminase b subunits function to control the rate of enzyme formation by thrombin (6).

The Ca^{2+} requirement for catalytic hydrolysis and transfer of active esters by plasma and platelet transglutaminases has been examined. It was surprising to find that this requirement (K_a, Ca^{2+} 50 mM) is significantly higher than that for amine incorporation at glutamine residues. The opposite has been found to be true with the tissue enzyme (7).

Active site mapping studies of transglutaminases, commenced last year, have been extended with particular emphasis on the tissue and blood enzymes. Earlier findings, using straight- and branched-chain aliphatic amides indicated that glutamine substrate attaches to the enzymes with its β and γ methylene groups situated in a hydrophobic binding region and with its carboxamide group directed toward the active site -SH group of the enzyme (8). The dimensions of this binding cleft on the enzymes were estimated from atomic model studies to be about 5A X 5A. Evidence has been obtained from inhibitor and kinetic studies that the enzymes undergo a conformational alteration at some step during catalysis, probably preceeding or together with enzyme acylation. These findings with aliphatic amides have been confirmed by using peptide derivatives of methylglutamine isomers (9). That the derivatives of L-α-methylglutamine only are substrates for transglutaminases is strong evidence for the postulated active sites. The observations with the methylglutamine derivatives have also formed the basis for a theory as to how the enzymes exert their stereospecificity, i.e., their strong preference for L-glutamine residues. This follows from the suggestion that peptide-bound L-glutamine residues are oriented on the enzyme surface with their α-hydrogen projecting away from the surface. In the case of D-glutamine residues the α-hydrogen, abutting the enzyme surface, perturbs the normal mechanism.

A series of heptapeptides of the general structure, X-X-X-L-gln-X-X-X, where X is glycine or L-leucine and L-gln is L-glutamine, have been prepared. The formylated derivatives of these peptides have been tested in an effort to gain evidence that transglutaminases have an extended active

site, and that the variations in specificity of the various classes of enzymes are a function of the amino acid residues surrounding the glutamine residue; the findings to date are very encouraging, and indicate pronounced effects of hydrophobic residues as far as three amino acid residues away from the glutamine (10). Reporter group studies are being conducted in conjunction with these activity investigations. Design and preparation of inactivator compounds that will report the position of hydrophobic binding sites are underway.

Active site mapping has been extended to studies on the primary amine binding sites in the acyl transglutaminases. As in the case of glutamine residues, there is a pronounced stereopreference for the ε-amino groups of L-lysine residues in peptides. Peptides containing L-lysine residues are bound approximately 5 times more tightly to the acyl enzymes than are those containing D-residues of lysine (11).

The specificity of activated blood coagulation factor XIII is under investigation. A series of synthetic peptides, of amino acid sequence similar to the nonvariable cross-linking region of fibrin, have been prepared and tested. Indications are that the sequence, L-gln-L-his, is most important for rapid catalytic activity of this cross-linking enzyme.

The sites and rates of synthesis and breakdown of the transglutaminases in vivo and in isolated cells is being studied using the rabbit. Early findings indicate separate sites of synthesis of the a and b chains of factor XIII and the particle-bound nature of the tissue enzyme.

Significance

A comprehensive study of various transglutaminases has shown that the enzymes are widely distributed in various organs and tissues, and that they may all be involved in the formation of ε-(γ-glutamyl)lysine cross-links within and between protein molecules (12). These linkages are essential in maintaining the permanent rigid structure of many protein molecules.

The physiological importance of the protransglutaminases of plasma and platelets is well known. The finding of protransglutaminases in placenta and uterus indicates another regulatory control site of the blood coagulation process. Estrogen and progesterone regulation of transglutaminase levels in rabbit uterus is under investigation as is hormonal control of synthesis in liver and spleen.

Understanding of the molecular characteristics of the transglutaminases is vital to determination of the function of these enzymes in normal and diseased tissues, pharmacological control of activity and hormonal regulation.

The minimal substrate structural requirements for liver transglutaminase have been defined over the past year through the studies described above. We now have a better understanding of the mechanism of enzyme-substrate

interactions in transglutaminase-catalyzed reactions. The technique of active site mapping using straight and branched chain substrate analogs, methylglutamine isomers, D- and L-lysine peptides and large glutamine and lysine peptide derivatives, is one which will be applied to studies with other transglutaminases and most certainly will reveal similarities, as well as differences, in the members of this important group of enzymes.

Future Plans

Preliminary studies suggest a primary role for transglutaminases in wound healing (for review see (1)). Attention will be focused on the possible interaction between fibrinogen and collagen as catalyzed by transglutaminases and the possible relationship of this interaction to wound healing.

The interrelationship between the fibrinolytic enzyme, plasmin, and transglutaminases may be of prime importance in chronic inflammation. Studies will be directed toward examining the influence of transglutaminase-catalyzed cross-linking on plasmin degradation of a number of structural proteins.

The possible use of liver transglutaminase in localizing and determining the orientation of membrane proteins and other structural protein is under investigation.

Studies of the effect of various amino blocking groups on the reactivity of model peptide substrates will be continued. The effect of various metal ions on these activities of transglutaminases will be investigated.

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Summary Report of the Protein Chemistry Section
Laboratory of Biochemistry
National Institute of Dental Research

Background

Collagen is the major structural protein of all vertebrate and many invertebrate species. It is found not only in the major connective tissues, skin, tendon, bone and cartilage, but is an important component of tissues such as basement membranes, cornea and blood vessels. The basic structure common to the major and many minor collagens is a rod-like molecule about 3000 x 15A composed of three polypeptide chains each with about 1000 amino acids. The major collagen of skins, tendon and bone (type I collagen) contains two kinds of chains (two α1 and one α2 chain) but other collagens have three identical chains that appear to be closely related to the α1 chain of type I collagen.

The collagen molecule is triple-helical throughout most of its length. However, the N- and C-terminal 15-25 amino acids do not have the characteristic amino acid sequence of the helical portion of the chains and therefore have a different structure. Covalent cross-links, derived from lysine residues, originate in these regions. They may also have other functions.

Collagen functions biologically as the fibril, an ordered rope-like array of molecules several hundred to several thousand angstroms in diameter. These fibrils are arranged in various ways characteristic of the tissue. At this level of structure, other constituents of connective tissue play important roles. These constituents vary with the tissue but often include elastin, the proteoglycans and mineral.

Elastin, as the name implies, forms an elastic tissue that is a major constituent of large blood vessels and certain ligaments and a minor constituent of many connective tissues.

Proteoglycans are major constituents of cartilage and minor but perhaps critical constituents of many other connective tissues. They are large macromolecules (MW 1-4 million) in which large numbers of the sulfated polysaccharide chains, chondroitin sulfate and keratan sulfate, are covalently bound to a core protein. Such a molecular architecture leads to macromolecules which occupy large hydrodynamic volumes and exhibit reversible compressibility, characteristics which help provide cartilages with resiliency, and resistance to compression. In cartilage, and probably in other tissues as well, the core protein of proteoglycans consists of two distinct regions. One end, the HA-binding region, consists of a portion of protein (MW about 80-90 thousand) devoid of polysaccharide which interacts in a highly selective way with hyaluronic acid and quite probably with at least one small molecular weight protein referred to as a "link" protein. These interactions are essential for the organization of proteoglycans into aggregate complexes in the tissue extracellular matrix. The remainder of the core protein in the proteoglycan, the polysaccharide attachment region,

contains an average of about 100 chondroitin sulfate and 50 keratan sulfate chains with about 60% of the latter concentrated in a region close to the HA-binding region. The polysaccharide attachment region of the core protein has a variable length depending upon its degree of substitution with polysaccharide chains.

Connective tissue studies involve not only chemical and structural investigations of the various constituents, but also interactions among them. These interactions are responsible for the structure, properties and biological function of the tissue.

Progress

Certain aspects of the broad problem outlined above are being emphasized in the current program of the Section. These aspects together with recent progress are discussed separately.

1. Soluble collagen as normally isolated is known to be altered by proteolytic cleavage of the C-terminal nonhelical region. The results of various chemical and physical-chemical studies using these preparations may therefore be effected by this alteration. Of particular interest are studies of fibril formation where the N- and C-terminal regions may play critical roles in directing aggregation. Methods to prepare intact soluble collagen are therefore being sought. Enzyme inhibitors can be used to prevent proteolysis. However, rapid extraction and purification with careful attention to details seems to work as well. Some tissues are also better sources of intact collagen since they have a lower protease content. Rat tail tendons have been found to be perhaps the best readily available source for large amounts of unaltered collagen.

2. Although most collagens that have been studied have the same basic molecular structure, other collagens or collagen-like proteins are known that have quite different structures in that large parts of the molecule are noncollagenous. These include procollagen (the biosynthetic precursor of collagen) (1), C1q (a complement component), possibly some of the basement membrane collagens and certain invertebrate collagens. One in the last group is Ascaris cuticle collagen. We are presently studying this protein to gain a better understanding of these "unusual" collagens. We have found that the reduced denatured protein contains three different chains that can be separated chronatographically. They all have collagenous and noncollagenous portions and molecular weights of about 60,000 (compared to 95,000 for the α chains of the common vertebrate collagens). The relative amounts vary widely in different samples suggesting that they are derived from three different collagens rather than from one collagen with three different chains. Current studies are attempting to relate the chains to the molecular structure.

3. The completion of the amino acid sequence of the α2 chain (2) permit a correlation between the sequence and the packing of collagen molecules in the fibril. A relationship between the primary structure and the staining characteristics seen by electron microscopy has been shown, and this has permitted a detailed analysis of several types of polymorphic collagen aggregates (3).

4. A more complete study of the three-dimensional order of collagen molecules in the native fibril has been done by analysis of electron micrographs of a collagen aggregate consisting of narrow native fibrils packed side-by-side but staggered by about 100 A (4). This produces a larger obliquely-banded fibril. This analysis supports x-ray diffraction evidence for the Smith microfibril (5). The Smith microfibril is essentially a helix of collagen molecules about 40 A in diameter. Microfibrils are believed to be aligned in parallel array to form bundles of varying size. These are the fibrils commonly seen by electron microscopy. This model explains some of the properties of collagen fibrils and permits the design of experiments on fibril formation (6).

5. Proton and ^{13}C magnetic resonance are powerful tools for studying molecular mobility and structure. This method was used to follow the helix-coil transition in a small peptide from collagen (7,8). Proton magnetic resonance is currently being used to follow readily identifiable amino acid residues such as tyrosine, phenylalanine and histidine in collagen to determine the structure of regions of the collagen molecule containing these residues. ^{13}C magnetic resonance is a more powerful tool for this kind of structural study if specifically ^{13}C-labeled material can be made. Currently, techniques are being devised to enrich collagen in a ^{13}C amino acid by biosynthetic incorporation of a labeled amino acid. This is necessary to obtain the sensitivity and specificity required for solution studies at moderate concentrations.

6. Elastin structure has been explored by ^{13}C magnetic resonance also. In this case, studies can be done in the solid state since elastin polypeptide chains in native elastic tissue are mobile like the chains in a natural or synthetic rubber. Addition of certain organic solvents in water increases chain mobility suggesting domains of hydrophobic interactions where mobility is inhibited. Computer analysis of spectral line widths show alanine resonances to be about ten times broader than those of glycine. Since alanine is known from chemical studies to be concentrated near the covalent crosslinks in elastin, while glycine occurs in regions between crosslinks, a model in which crosslink regions are relatively fixed in position and the interconnecting chains are mobile and essentially random coils, but tend to form hydrophobic domains seems reasonable. The molecular basis for the mechanism of elasticity in elastin is therefore similar to that in rubber but deviates from ideal behavior under physiological conditions is not being completely free of chain-chain interactions.

7. Proteoglycan studies are just beginning in the Section. The starting point will be studies done elsewhere on proteoglycan structure, aggregation and biosynthesis as recently reviewed (9).

Significance

Since collagen and the proteoglycans are the major structural constituents of connective tissues including teeth, bone, cartilage and supporting oral structures, knowledge of their chemistry and structure is necessary to an understanding of normal function. This understanding will permit a rational approach to the understanding and, thereby, to the prevention and treatment of

connective tissue diseases. These include caries and periodontal disease, the major diseases of oral tissues. Progress along these lines has led to major programs in many laboratories studying orthopedics, dermatology, rheumatology, genetic disorders, and calcification, wounnd healing, inflammation, ageing and pulmonary disease as well as oral disease.

Future Plans

Studies will continue on all of the projects reviewed above. The study of methods to prepare intact soluble collagen and the magnetic resonance studies of elastin are nearing a normal conclusion. Emphasis will be placed on: 1. studying in more detail the structure of the collagen fibril using chemical methods, electron microscopy, ^{13}C magnetic resonance and computer modeling to examine the relationship between primary structure and molecular packing; 2. devising systems and methods to study fibril formation in vitro; 3. the study of fibril formation when these first experiments provide the techniques; 4. studies on the chemistry and biosynthesis of the core protein of proteoglycans; 5. the nature of the hyaluronate-binding region of proteoglycans; 6. establishment of ultramicro methodology to study proteoglycans in small tissue samples; 7. the interaction between proteoglycans and collagen.

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Summary Report of the Laboratory of Biological Structure
National Institute of Dental Research

This year was the first year of operation for the Laboratory of Biological Structure after consolidation of its functional mission to the program areas of mineralization and salivary gland function. In spite of its limited size, the laboratory has continued to maintain a gratifying level of research accomplishment. The research has covered a series of basic investigations with the common goal to facilitate understanding of a variety of normal and abnormal biological processes affecting oral health. As in prior years progress for the year is reported in the sectional summaries which follow.

During the reporting year the professional staff of 5 senior investigators, one staff fellow and one visiting fellow have submitted nine manuscripts, one of which was a chapter for a text book, and eight abstracts for publication. In addition members of the staff have participated in national and international meetings and workshops; in editorial tasks; and in scientific review functions relating to NIH and other granting agencies. Members have also been active in scientific organizations and have played an important role in the operation of the newly established Mineralized Tissue Group within the International Association for Dental Research.

This year a number of additional positions was made available to the laboratory to provide the necessary critical mass to its programs. Efforts to fill these positions with competent scientists with background and experience covering specific areas of science have largely been successful. In addition the laboratory has been asked to sponsor several post-doctoral fellows. If these fellowships are awarded, the professional staff of the laboratory will shortly number six senior investigators, four staff fellows, one visiting fellow and three post-doctoral fellows. This additional expertise and manpower coupled with that already present in the laboratory and that available through collaboration with the Laboratory of Biochemistry will make it possible to mount a much more concerted effort in both program areas.

Summary Report of the Experimental Morphology Section
Laboratory of Biological Structure
National Institute of Dental Research

The basic objectives of the Experimental Morphology Section are to advance knowledge concerning the structure and function of normal and experimentally altered tissues and cells. Light and electron microscopy, electron diffraction, microradiography, enzyme cytochemistry, extra- and intra-cellular tracers as well as specific chemical detection methods are the principal techniques which are used.

Studies presently underway include: (1) the effect of tetracycline hydrochloride on the development of mineralized tissues in the rat; (2) mineralization processes in rat tail epiphyseal plate and tendon; (3) ultrastructure and cytochemistry of salivary glands and (4) the handling of exogenous materials by the rat parotid gland. This summary report describes progress made in some of these studies in more detail.

To-date our experiments have shown that the effect of tetracycline hydrochloride (TC) on tooth development in any age group is directly related to the total dose and to the concentration at which the drug is administered. Both of these effects, in turn, were shown to be directly related to serum levels of the drug. Comparisons between age groups revealed that the response to the drug fluctuates with age. Determinations of serum levels in two of the groups, the four- and seventy-five-day-old animals, revealed that the drug was cleared much more slowly from the serum of the small rats. This difference in clearance rate did not appear to be critical in experiments comparing the effect of single injections of the drug. On the other hand, it could be the main reason why multiple injections of the antibiotic as reported in the literature affect teeth of small animals much more severely than those of older animals. Presumably the drug eventually reaches a higher plateau in the serum of the small animals because of the lower clearance rate.

To test this concept, seventy-five-day-old animals were given multiple intraperitoneal injections with TC at intervals of either six or twenty-four hours while four-day-old rats were dosed every twenty-four hours. The dose selected was one which was known not to cause defects in either of the two age groups when administered singly. The six hour interval was chosen because at this time serum levels in the old rats are similar to those measured twenty-four hours after dosing in the small animals. Examination of the teeth by fluorescence microscopy and microradiography revealed that all the four-day-old as well as the seventy-five-day-old animals on the six-hour schedule developed gross lesions in their teeth. On the other hand, the teeth of the adult animals on the twenty-four-hour schedule were not affected in this manner. These results indicate that the sensitivity of the small animal is due to the low rates at which the antibiotic is cleared from the serum. In this connection it is interesting to note (1) that new-born children have been shown to have a slower serum clearance rate for TC than older children and (2) tnat new-born children also exhibit a higher incidence of TC-induced dental defects than older children.

Future efforts will be directed to studying the effect of TC on bone and dentin formation using both in vitro and in vivo model systems with the purpose of gaining insight into the drug's mechanism of action both at the cellular and extra-cellular levels.

Systematic morphological examination of the salivary glands is being undertaken so as to provide a clearer understanding of the correlation between structure and function of secretory cells. Although the major portion of the investigation is conducted on the rat parotid gland, other salivary glands and related exocrine organs are utilized when it is felt that they may provide additional information or serve as a particularly suitable model system.

Much of the effort this past year has been directed toward the continuing study of the cytochemistry of the Golgi apparatus in exocrine cells. Most of this work was carried out using the rat exorbital lacrimal gland, primarily because of the resistance of its secretory peroxidase to gluteraldehyde fixation. The results indicate that the Golgi apparatus is extremely large in these gland cells although the morphology essentially is the same as in the parotid gland. In attempting to sort out spatial and functional relationships between the various components of the Golgi apparatus in the lacrimal cells, it became apparent that the portion which is reactive for acid phosphatase is expecially extensive, much more so than in other exocrine gland cells previously examined.

Studies are also underway aimed at elucidating the fate of secretory granule membranes added to the proximal membrane of secretory cells during granule discharge. Tracer materials detectable by electron microscopy (horseradish peroxidase, ferritin, tyrosinase) are injected retrograde through the main duc of the rat parotid gland and allowed to be taken up by acinar cells. Preliminary results suggest that characteristic doughnut-shaped vesicles pick up the tracer at the luminal surface and carry it back mainly to lysosomes. This indicates that at least part of the discharged granule membrane may be broken down by the cells. Comparisons of tracer uptake by the cells after i.v. injections are in progress as are investigations involving retrograde injections following stimulation of secretion.

Studies of peroxisomes and microperoxisomes in the salivary glands have yielde interesting results. In the cells of the striated, interlobular and main duct of the mouse submandibular gland, the peroxisomes are very large and numerous and apparently have a high content of catalase. They also appear to be labile to fixation, since the catalase seems to leak out of the peroxisomes and diffuse throughout the cells. In the other salivary glands of the mouse these large, leaky peroxisomes are restricted to the larger interlobular and main ducts, and a similar distribution has been found in the rat. The duct cells also have a moderate amount of smooth endoplasmic reticulum, and the large numbers of peroxisomes in these cells suggest a possible participation in steroid synthesis and metabolism.

Future plans are to continue studies of various secretory cells in order to elucidate further the role of the different organelles in the function of normal and experimentally altered cells. In addition to cytochemical techniques, immunocytochemical studies will be initiated aimed at identifying the cellular pathways of the secretory proteins and secretory immunoglobulins. Studies will also be initiated concerned with the establishment of cell culture methods with differentiated exocrine cells. Attempts will be made to obtain pure lines of various cell types of the glands to allow analysis of cell functions. The results will be compared to data obtained by other *in vitro* techniques such as the use of dissociated cells and tissue slices.

Summary Report of the Molecular Structure Section
Laboratory of Biological Structure
National Institute of Dental Research

The principal objective of the Molecular Structure Section is to study the physical-chemical and ultrastructural properties of calcified tissues, their collagenous and mineral components, and related synthetic systems. This past year's research efforts were primarily focused on a number of calcium phosphate compounds of biological interest, especially amorphous calcium phosphate (ACP) and crystalline apatite (CA) - the two principal constituents of hard tissue mineral.

In recent years, a number of studies have provided experimental evidence for the co-existence with apatite of an amorphous mineral phase in calcified tissue. Parallel *in vitro* studies have established that ACP is a precursor phase in the *de novo* formation of apatite from homogeneous solutions. Based on such evidence, it has been postulated that initial apatite formation *in vivo* is preceded by an amorphous intermediate. Most biological mineralization, however, occurs along fronts already containing apatite crystals. To assess the possible effect this apatite layer may have on *in vivo* calcification, studies have been undertaken to examine the *in vitro* formation of calcium phosphates from solutions seeded with apatite.

Results obtained during this past year showed that supersaturated solutions stable to spontaneous ACP formation underwent a two step loss in solution calcium and phosphate when seeded with apatite. The initial fraction of calcium and phosphate removed from solution appeared as an amorphous accretion on the surface of the seed crystals. This instantaneous event was followed by the much more gradual formation of new apatite crystals overlaying the original seeds, accompanied by a further, exponentially decreasing, reduction in solution calcium and phosphate. Kinetic data suggest, however, that this secondary crystallization step commenced almost immediately with no apparent induction period. Therefore, the amorphous surface coat on the apatite seeds does not appear to play the same retarding intermediary role in apatite formation as does free ACP.

Physiologically-balanced salt solutions were also found to be unstable when seeded with apatite, with losses in solution calcium and phosphate occurring in a manner similar to that just described. This finding suggests several possible biological consequences: (1) Once apatite crystals have become established at a calcification site in hard tissue, further mineralization may proceed by direct crystallization of new apatite crystals without the necessity of an ACP intermediate. However, this conclusion does not negate the possible obligatory role of ACP in initiating calcification. (2) The ACP present in calcified tissues, especially mature tissue, may be in the form of an amorphous coat on the apatite crystals. (3) Extracellular fluid levels of calcium and phosphate may be unstable upon contact with apatite suggesting the presence of stabilizing factors *in vivo* preventing unwanted mineralization.

Not only are physiological fluids immediately unstable in the presence of apatite, but, as reported in previous summaries, they also appear to possess the potential to form mineral de novo. The induction of the initial amorphous phase in these cases is considerably protracted in time and the resultant yields are slight (less than 5%). But if this initial step is followed by conversion to apatite, then these fluids would exhibit the same instabilities as if exogenously seeded. Studies conducted during the past year suggest, however, that many metabolic intermediates and biopolymers can inhibit this second step leading to the formation of apatite. It was found that de novo apatite formation from balanced salt solutions can be blocked by glycolytic diphospho-intermediates, and di- and triphosphate nucleotides in concentrations as low as 10^{-5}M. Phosphoproteins and acidic biopolymers are also effective as inhibitors at 0.2 mg/ml levels. Inhibition can be abolished by digestion of the treated amorphous intermediates with alkaline phosphatase and/or proteases, thus suggesting possible enzymatic control mechanisms for tissue mineralization.

Long standing sectional activities in the structural characterization of hard tissue mineral and related synthetic analogues have recently culminated in the publication of a definitive infrared spectroscopic analysis of the vibrational spectra of hydroxyapatite (B. O. Fowler, Inorg. Chem. 13:194-207,207-214, 1974). One application of this cataloging of hydroxyapatite spectral lines will be the use of vibrational spectra for more accurate and quantitative description of the important bonding interactions between the ionic constituents of the apatite lattice. As an example, the recent identification of the vibrational origin of several lattice mode lines for hydroxyapatite is important for identifying and studying anionic substitutions and interactions along the hexad axis of the apatite lattice. Extension of these spectroscopic studies to the Raman and far-infrared regions has shown that stoichiometric, high-purity hydroxyapatites are not hexagonal but are generally monoclinic in symmetry. On the other hand, impure, non-stoichiometric hydroxyapatites, such as encountered in biological systems, are hexagonal. The knowledge of such atomic-scale details as just described will greatly strengthen our understanding of the relevant physicochemical actions of biological apatites and will provide us with a more rational basis for chemically altering hard tissue mineral to our therapeutic advantage.

Various members of the section's staff were engaged in several collaborative efforts during the past year. In conjunction with R. A. Peckauskas and I. Pullman of New York Medical College, an electron spin resonance study was completed this past year on acidic biopolymer-mineral bonding via the use of VO^{2+} probes. It was found that apatite binds to the carbonyl groups of glutamyl and aspartyl polymers and to the serine phosphate residues of egg yolk phosphoprotein (phosvitin). In chondroitin sulfate complexes, apatite binds with the sulfate groups. In an x-ray diffraction study with L. Avioli and J. Russell of Washington University School of Medicine, St. Louis, on the efficacy of vitamin D metabolites and diphosphonates as drugs to treat chronic uremic rats, it was found that each drug alone reversed the uremic effect of retarding bone mineral maturation but they were most effective in combination. A collaborative effort with R. Wuthier of the University of Vermont revealed that acidic phospholipids such as phosphatidyl serine had significant stabilizing effects on ACP, markedly delaying the latter's conversion to apatite.

Phosphatidyl serine was more effective when added to preformed ACP than when present during ACP precipitation indicating that the blocking effect of the lipid was surface controlled.

It is anticipated that the calcium phosphate studies will be continued with an attempt to further define the role of inhibitors in regulating calcium phosphate formation in seeded systems. Other continuations of current research efforts will include extensions of (1) the x-ray diffraction work on drug and hormone effects of osseous tissues, (2) electron spin resonance studies on biopolymer-mineral interactions (with expansions to include nuclear magnetic resonance and Laser Raman spectroscopy techniques), and (3) spectroscopic studies on enamel apatite and synthetic analogues.

Laboratory of Microbiology and Immunology
Summary Statement

The research programs in this Laboratory continue to focus on those problems which are appropriate and meaningful to the mission of NIDR and are relevant to biomedical research in general. This fact is attested to by the active participation of our investigators during the past year in not only dental research meetings but in other national and international meetings such as the Second International Congress of Immunology, New York Academy of Science conference on mechanisms of tissue destruction in rheumatoid arthritis, West Coast Conference on bacterial physiology, Midwinter Conference of Immunologists on soluble mediators and the immune response, Leukocyte Culture Conference, Annual Meeting of the Infectious Diseases Society of America and the American Society of Microbiology conference on pathogenic mechanisms in infectious diseases. In addition, an international conference on "The role of mitogens in immunobiology" has been organized by program leaders in our cellular immunology section. This meeting will convene at Airlie House in Warrenton, Virginia in May of this year and the proceedings will be published by Academic Press.

The Laboratory continues to seek application of its fundamental research through research protocols in clinical immunology and by strengthening its collaboration with the caries prevention and research branch of the National Caries program. Various streptococcal cell wall antigens and enzymes responsible for extracellular polysaccharide synthesis are being evaluated as potential vaccines in the prevention of dental caries. The programs in clinical immunology have made a rapid start in defining protocols which are relevant to underpining etiologic and immunopathologic mechanisms in oral soft tissue diseases. This group requires additional support in order to identify individuals who could be given an assignment in the dental clinic and who would combine their clinical background with research in clinical immunology. This would help integrate the clinical and laboratory efforts and consolidate clinical investigations in NIDR.

In March of this year an ad hoc committee was appointed by the Acting Director of Intramural Research to examine in depth the programs of the reorganized LMI. The committee was comprised of seven individuals, three of whom are members of the NIDR Scientific Board of Counselors with expertise in oral microbiology, microbial biochemistry and immunology. A detailed report of the examination was prepared by the committee and will be made available to the Institute Directors, Laboratory and Branch Chiefs and the Deputy Director for Science of NIH.

As in the previous year the detailed narratives and bibliographies on research progress are presented according to section designations.

Summary Report of the Cellular Immunology Section
Laboratory of Microbiology & Immunology

The immune response consists of a complex interaction between three major cell types, the B-lymphocyte, the T-lymphocyte and the macrophage. T-lymphocytes have several distinct and important functions. They are the cells that are responsible for cell mediated immune responses such as graft-rejection, tumor cytotoxicity and delayed hypersensitivity skin reactions. T-cells also act as "helper" cells for other immune responses, are "memory" cells and also regulate the immune response by a "suppressor" function. B-lymphocytes consist mainly of those cells that produce antibodies or their precursors. However, they are not limited to this role. Recent work has demonstrated that they act as "killer" cells for antibody-dependent cytotoxic reactions, and that they also produce lymphokines, the soluble products that are thought to mediate delayed hypersensitivity reactions. This ability to elaborate lymphokines was formerly thought to be limited to T-lymphocytes. The third cell type, the macrophage, is different from the lymphocyte in that it does not by itself demonstrate antigenic specificity. Rather, it acts as a non-specific accessory cell, to enhance and regulate the immune response of both B and T lymphocytes. It also has an important role in helping to eliminate invading organisms, especially those that are primarily intracellular.

Chronic inflammatory diseases are the result of an immune response in the tissue directed against foreign substance which in most cases remain unidentified. In a variety of ways, this immune response whose primary aim is to eliminate this foreign substance, results in the destruction of host tissue as well, in the form of an "innocent bystander" reaction. The inflammatory lesions of chronic inflammatory diseases probably contain all three of these cell types, T and B lymphocytes and macrophages.

Periodontal disease is unique among the chronic inflammatory diseases for several reasons. First, it is extremely common. Secondly, the deseased tissue is easily accessible for study. Finally, and most importantly, in contrast to most other diseases of this type, the etiologic agent of periodontal disease is known. In periodontal disease, plaque is the foreign substance against which the host damaging immune response is directed. Thus, using periodontal disease as an experimental model, it is the purpose of the cellular immunology section to study the mechanisms of activation of these immune cells, to learn the pathways by which they interact and finally to understand the way in which this host response ultimately produces the lesions chronic inflammation.

Macrophages and T Lymphocyte Activation

A large amount of effort has been devoted to studying the role of macrophages in the induction of lymphocyte activation for two reasons. First, because the macrophage plays such a pivotal role in the immune response and secondly, because this cell is so prominent in all inflammatory responses including those of Periodontal disease. We have found that the macrophage is required for T-cell activation by all stimuli including

mitogens, antigens and allogeneic cells (the mixed lymphocyte reaction). Using a cell purification technique that involves adherence to nylon wool we can prepare a highly-purified T-cell subpopulation. These T cells no longer proliferate in vitro (as measured by the incorporation of ^{3}H-Tdr into new DNA) in response to the T-cell mitogens, Concanavalin A (Con A) or phytohemmaglutinin (PHA), but will respond normally when reconstituted with small numbers of fresh macrophages (1-10%). Macrophages function in two ways to induce T-cell activation by PHA. They actually bind the PHA and then present it to the T-cell in a stimulatory form. They also release a soluble factor, called lymphocyte activating factor (LAF) that will help activate T-cells that have already bound PHA directly. It is likely that these two macrophage actions occur simultaneously in vitro. Macrophages also act in somewhat different ways under other experimental situations. It has been found that the macrophage acts as a powerful stimulator cell in the MLR. Certain oxidizing agents such as sodium periodate and the enzyme galactose oxidase, are T-cell mitogens and are macrophage-dependent as well. These agents have been found to act primarily on the macrophage and not the T cell, so that in a manner analogous to the MLR, it is the oxidized macrophage that actually is the stimulant in this case. Thus, in addition to being required for all forms of T-cell activation, the means by which macrophages act appears to differ and depend on the nature of the stimulating agent.

The Role of B Lymphocytes in Cell Mediated Immunity and Their Mechanisms of Activation

The predominant cell types in chronic inflammatory lesions especially those of chronic periodontitis are plasma cells and other cells of the B lymphocyte series. Until recently, it has been difficult to reconcile the presence of these antibody-forming cells with the presumed pathogenesis of periodontal disease which involved cell-mediated immune processes. Consequently, a great deal of effort has been spent in trying to determine the relationship of B-lymphocytes to cell-mediated immunity.

B cells differ from T cells in that they require T-cell "help" to respond to certain types of stimuli. However, there are a large number of stimulating agents that will activate B cells directly without T cell help. These agents are referred to as thymic-independent stimuli and are especially important in the pathogenesis of periodontal disease since many components of plaque such as polysaccharides, lipopolysaccharides and other bacterial cell wall components are classical T-independent stimulants.

It has been found that a capsular polysaccharide from Klebsiella (CPS-K); lipopolysaccharides, polynucleotides as well as teichoic acid from gram-positive bacteria are all mitogenic for B-lymphocytes in the mouse as judged by their ability to activate purified splenic B cells as well as spleen cells from athymic ("nude") mice. They also fail to activate purified mouse splenic T-cells. Some of these compounds have also been found to induce lymphokine synthesis in mouse or guinea pig B-cells.

Since B-lymphocytes have been found to produce lymphokines, which are thought to be the mediators of delayed-hypersensitivity, B cells should

be able to induce true delayed hypersensitivity. An in vivo model has been developed to test this hypothesis. Guinea pigs immunized to the antigen DNP-KLH will manifest strong DH skin lesions when tested with the T-independent antigen DNP-Ficoll. We have found that in vitro, lymphocytes from these immune guinea pigs will produce the lymphokine monocyte chemotactic factor, in response to DNP-Ficoll. Furthermore, only B and not T lymphocytes respond in this fashion. This observation suggests very strongly that B cells may play an important role in DH in vivo depending on the nature of the inciting agent.

The mechanisms by which T-independent antigens activate B cells has also been investigated. The mitogenic activity of LPS has been found to reside in the lipid A fraction. Furthermore, B cell activation by lipid A seems to be the result of a physical-chemical interaction between the lipid and the cell surface, since a simple, synthetic glycolipid, N-palymitoyl-D-glucosamine, has been also found to be a B cell mitogen in mice. However, it is not yet understood how this interaction results in lymphocyte activation. One hypothesis is that endotoxin and related lipophilic compounds act as calcium ionophores and trigger cells by raising intracellular calcium levels. To test this hypothesis, the ionophoric activity of several known B cell mitogens was tested. It was found that the macromolecule protein keyhole limpet hemocyanin (KLH) as well as lipid A and an endotoxic glycolipid (MR 595) all acted as ionophores. In addition, a known protein ionophore, excitability inducing material (E.I.M.) was also found to be a potent B cell mitogen. Thus, these findings are consistent with the idea that endotoxin acts as a B cell mitogen by raising intracellular calcium levels.

Since many of the inciting agents of chronic inflammatory diseases are probably thymic dependent antigens, we have also studied the mechanisms behind the phenomenon of T-cell "help". B cell activation has been measured by the numerical increase in antibody-forming cells by the Jerne plaque assay. Using a Marbrook culture system where it is possible to separate different cell types within the same culture vessel, it has been found that T-cells release a soluble factor that enables B cells to respond to T-dependent antigens. T cells release this factor when activated by either specific (antigen) or non-specific (allogeneic cells) stimuli. Furthermore, this factor lacks species-specificity since a soluble factor derived from human T-cells will help activate murine B-cells.

Endotoxin and its Interaction with Lymphoid Cells

Bacterial lipopolysaccharides (LPS) exert a large number of diverse effects on many biological systems. Recent work has demonstrated that LPS acts on B lymphocytes and macrophages and may also influence T-lymphocyte activation as well. Since LPS is present in large amounts in plaque, we have investigated some of the ways this compound interacts with lymphoreticular cells in order to better understand the role LPS plays in the pathogenesis of periodontal disease.

An assay to measure macrophage activation was developed utilizing the uptake of C^{14}-glucosamine by macrophages. LPS induced macrophage activation in vitro was measured by this parameter as well as by others such as the release of lysosomal enzymes. However, it was found that LPS does not act directly on the macrophage to induce uptake of C^{14}-glucosamine. Instead, LPS activates B lymphocytes which in turn release a lymphokine, macrophage activating factor (MAF) which then activates macrophages. This mechanism may be one way that endotoxins in plaque maintain a state of chronic inflammation in the gingival tissues.

Certain strains of mice are unresponsive to some or all of the biological effects of LPS. The cellular basis and genetics of LPS unresponsiveness have been studied in some detail. C3H/HeJ mice are unresponsive to LPS while a closely related strain, C3H/HeN are good responders. These mice are completely identical at the H_2 locus since they do not exhibit reciprocal mixed lymphocyte reactions, graft vs. host reactions or reject reciprocal skin grafts. Since they do not recognize each others cells as foreign, it is possible to reconstitute non-responder mice with responder spleen cells and obtain an LPS responsive chimera. Using cell isolation, purification and mixing techniques in vitro we have established that the defect in C3H/HeJ mice resides in the B lymphocyte and that unresponsiveness is not due to the absence of a critical accessory cell or the presence of some suppressor cell. In fact, the interaction of LPS with the non-responder B cell appears to directly suppress its response rather than cause activation. Unresponsiveness is also not due to a B cell deficiency or the numerical absence of some B cell subpopulation since C3H/HeJ B cells appear to be identical to C3H/HeN B cells when examined by several different surface marker techniques. This contrasts with the situation in another non-responder mouse strain, the CBA/HN, which is clearly deficient in B cells.

The genetics of LPS unresponsiveness has also been studied using the previously identified strain combinations. LPS responsiveness in C3H/HeN mice appears to be controlled by a single autosomal gene that exhibits co-dominant expression. In contrast, LPS responsiveness in CBA/HN mice which exhibit on absolute deficiency in numbers of B cells, is controlled by an x-linked recessive gene. Evidence that these two defects are controlled by separate genes is given by the fact that some F1 hybrids of two non-responder parents are responsive to LPS in vitro.

A study on the nature of the LPS receptor on lymphocytes (if at all present) has been recently undertaken. Unlike T cell mitogens such as PHA, LPS has to be present continuously in culture to produce maximum mitogenesis suggesting that the LPS receptor is either of low affinity or that activation requires a constant renewal of LPS-receptor contacts. Using C^{14}-LPS we have found that the binding of LPS to macrophage-depleted spleen cells occurs within one hour at 37°C and increases slowly with time in culture up to 48 hrs. Purified B cells bind more LPS than do purified T cells. Preliminary evidence suggests that spleen cells from non-responder C3H/HeJ mice bind as much LPS as those from C3H/HeN mice, suggesting that LPS unresponsiveness is not due to a defect in binding of LPS.

Interaction Between Mediators of Acute Inflammation and Lymphoid Cells

Although it is clear that there exists a complex interaction between all the cells of the lymphoid system, much less is known about the interaction of soluble mediators of acute inflammation such as serotonin, histamine and bradykinin and inflammatory cells. We have found that one such mediator, serotonin, will interact with human peripheral blood lymphocytes to cause production and release of the lymphokine, monocyte chemotactic factor (MNL-CTX). The dose response to serotonin is very narrow and other related compounds are inactive. MNL-CTX production does not occur until 48 hrs after serotonin stimulation but then continues for up to 144 hrs in culture. The chemotactic factor produced in culture is non-dialysable and is not therefore a low molecular weight metabolite of serotonin but is probably a lymphokine. The nature of the cell responsible for this response is currently being investigated. Preliminary data demonstrates that purified T-cells by themselves do not produce MNL-CTX when stimulated by serotonin. In other studies, it was found that serotonin induced a rapid rise in macrophage intracellular cyclic GMP. The relationship between this phenomenon and the production of MNL-CTX is currently being explored.

The Role of Food Products in the Pathogenesis of Periodontal Disease

A common observation by dental practioners has been the presence of corn particles in periodontal abscesses, often occurring in relatively healthy mouths. This phenomenon stimulated the premise that corn may possibly be mitogenic, and rather than acting as a vehicle for bacterial penetration, or as a nutritional substrate for bacterial proliferation, may well be a major contributing factor to the abscess through the mitogenic activation of lymphocytes. We therefore, tested the *in vitro* lymphoproliferative response of peripheral human lymphocytes to detect possible cell mediated immunity to components of corn and nuts. However, rather than indicating antigenic sensitization, our findings indicate that these seeds contain nonspecific mitogenic activators of all adult and cord blood luecocytes. These mitogenic components may contribute to the pathogenesis of periodontal disease. Chemical isolation and characterization as well as cell specificity studies on this mitogen are currently underway.

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Summary Report of the Clinical Immunology Section
Laboratory of Microbiology and Immunology
National Institute of Dental Research

The Clinical Immunology Section was created in April 1973 to integrate basic with clinical immunological studies. The section also carries a service responsibility in that the two clinical associates are responsible for the medical workup of patients in the dental clinic and for the care of any patient admitted to the NIDR hospital beds. Therefore, the clinical associates, on the average, spend 25% of their time in this type of responsibility. The research aim of this section is to define humoral and cellular mechanisms of immunological tissue injury. For this purpose, we are exploring cellular and humoral mechanisms in animal model systems of immune injury, and their possible manipulation, while at the same time applying similar techniques to clinical studies in humans.

The cellular mechanisms involved in autoimmune reactions were studied in patients with Sjogren's syndrome. These patients develop widespread lymphoid infiltrates in many organs and a large proportion of such lymphocytes have been identified as B cells. The possible etiological role of immune response genes was investigated by tissue typing all patients who fulfill the diagnostic criteria for Sjogren's syndrome. Interestingly, 60% carry the HL-A8 antigen compared to 20% of normals. Statistically this difference is highly significant. This same antigen, HL-A8, is increased in a number of other autoimmune diseases, suggesting a common underlying genetic abnormality. Whether HL-A8 *per se* or the closely linked immune response region is involved remains to be determined. Similarly, periodontal patients are currently being tissue typed to see if they have any disturbance in antigen frequency.

New Zealand mice are a useful experimental model for autoimmune disease and mimic some of the pathological findings of Sjogren's syndrome. Investigations are attempting to define the cellular immunological abnormalities in these mice. Spleen lymphocytes from this strain, and its F_1 hybrid, NZB X NZW, do not respond normally *in vitro* to the thymic dependent antigen sheep erythrocytes. This defect is present by 5 weeks of age, long before overt autoimmune disease appears. The respone to DNP-Ficoll, a thymic independent antigen is normal. The sheep red cell response is restored by 2-mercaptoethanol, allogeneic marcrophages, or soluble allogeneic factor. NZB macrophages appear to function normally *in vitro*. These experiment suggests a defect in the usual mechanism of T-B cell collaboration *in vitro*, which may well be related to the development of autoimmune disease later in life.

The nature of the compounds which can activate basophils for histamine release is under study. A series of bivalent haptens with the general formula R-NH-$(CH_2)_n$-NHR' was used to test for histamine release from basophils. Monovalent haptens (R'=H) were inactive whereas the bivalent haptens (R=R') were active in releasing histamine even when n was as small as 3. The most active compounds were n=6-9 and these were as active as a multivalent compound. Longer chain compounds (n=12) were less active. However, when the two BPO groups were separated by rigid diphenyl bridges, the longer chain compounds were equally active. The bivalent haptens were as active on a molar basis as a multivalent compound. Similarly, a compound which has two different haptens at R' and R

is active only on basophils which have been obtained from animals immunized with both haptens. The addition of supraoptimal amounts of bivalent hapten results in a decrease in the histamine release. This is due to lack of bridging of IgE molecules; the excess bivalent hapten does not affect the activation of the cell by an unrelated antigen. The results are interpreted to indicate that activation of a basophil is due to bridging of two molecules on the cell surface with the resultant formation of a dimer. The evidence suggests that bridging does not occur within the two Fab portions of a single IgE molecule. It also indicates that the hapten binding sites on some of the IgE molecules must be very shallow.

Experimental studies are utilizing the plant lectin, concanavalin A (Con A) to investigate the mechanisms involved in the activation of basophils to release histamine and other mediators of inflammation. Con A induced histamine release from the basophils or mast cells of several mammalian species including human, rabbit, guinea pig, mouse, and rat. The mechanism was investigated in detail in humans. The optimum release was produced with 1 to 3 μg/ml of Con A. The response is characterized by inhibition by excess amounts of Con A and has great similarity to antigen or anti-IgE activation of basophils. The release of histamine by Con A requires Ca^{2+}, is modulated by the level of cyclic AMP, is inhibited by chlorphenesin and diethylcarbamazine and enhanced by deuterium oxide. The activation of the basophil depends on the binding of Con A to pyranosyl sugar residues on the cell membrane. It is characterized by a two stage reaction: the initial stage being the binding of Con A to the cell and the second stage being a secretory process of the cell. Cells desensitized by incubation with excess amounts of Con A or by erolonged incubation in the absence of cations cannot be activated to release with antigen or anti-IgE. When the native (tetravalent) Con A molecule is modified by succinic anhydride to become divalent it is much less active in releasing histamine. There is wide variation in the response of cells from different individuals to Con A. However, a close correlation exists between the histamine release induced by Con A and anti-IgE. Therefore, in general, cells from allergic donors release more histamine with Con A than th se from non-allergic individuals. It was established that Con A acts by binding to carbohydrate groups on the IgE molecule located on the basophil membrane. On a molar basis IgE is 4,000 fold more active than α-methyl-D-mannoside in inhibiting the Con A induced histamine release. Succinyl Con A blocks the ability of Con A and anti-IgE equally well and to a lesser extent the ability of antigen to activate cells to release histamine.

The role of complement (C) in histamine release is being investigated. The incubation of zymosan, endotoxin or immune aggregates with normal human serum activates a factor which induces release of histamine from autologous basophils. The reaction can be divided into two steps: in the first, complement must be activated and in the second, the histamine releasing factor interacts with basophils. The generation of histamine-releasing activity in serum occurs at 17-37°C but not at 0°C, is inhibited by heating the serum at 56°C for 30 min or by the addition of EDTA to the serum. Once generated, the histamine liberating activity is stable to heating at 56°C for 30 min. Gel filtration of the activated serum demonstrated that this factor eluted in the same region as a factor with chemotactic activity. Both factors have a molecular weight of about 16,000 daltons and their activities were inhibited

by antibody to human C5. This is therefore a pathway for histamine release where the activation of the basophil is unrelated to the membrane-bound IgE. The mechanism of the C5a induced histamine release is being investigated and compared to antigen-IgE mediated activation of basophils. The release reaction requires Ca^{2+} and is inhibited by EDTA. Both C5a- and antigen-induced histamine release are inhibited by diethylcarbamazine and chlorphenesin. Unlike the IgE-mediated reaction, C5a-induced histamine release occurs rapidly (it is 75% complete in 2 min.) The C5a reaction has a different pH optimum than antigen-induced release and occurs well at 17-37°C but not at 0°C. Antigen-induced histamine release does not occur at 25°C or below. In contrast to the antigen-mediated reaction, release by C5a is not enhanced by deuterium oxide. It is markedly enhanced by 10^{-6}M cytochalasin B. Preincubation of washed leukocytes in buffer at 37°C for 45 min renders the cells unresponsive to release by C5a but has no effect on IgE-mediated reactions. Cells from allergic donors incubated with antigen in the absence of cations (to render them unresponsive) release histamine normally upon the addition of C5a. The results indicate that histamine release by C5a involves a mechanism of basophil activation that is different from the pathway involved in IgE induced reactions.

Recent interest has focused on the use of ionophores as probes into the role of Ca^{++} in the coupling of secretion to membrane phenomena. Studies with the compound A23187, a Ca^{++} specific ionophore which transports this ion through the membrane, are attempting to better define IgE mediated cell activation. Ionophore A23187 releases histamine from normal mast cells apparently by promoting Ca^{++} influx. At concentrations of >0.2 µg/ml release occurs in 1-2 min, is blocked by metabolic inhibitors and is unaccompanied by cytotoxicity (trypan-blue uptake, lactic dehydrogenase (LDH) release). At higher doses (>0.5 µg/ml) histamine release is followed by significant cytotoxicity but again Ca^{++} is required. In parallel studies, we examined cultured rat basophilic leukemia (RBL-1) cells. These cells have apparently normal surface receptors for IgE, contain ~700 ng histamine 10^6 cells but did not release histamine when IgE-mediated release was looked for. They do not respond to doses of ionophore which would be expected to give non-cytotoxic histamine release. At higher doses histamine release is preceded by progressive LDH release: LDH release is 75% complete at 5 min whereas 10 min are required for 75% maximal histamine release. This reaction requires Ca^{++}, is temperature dependent but is uninhibitable by metabolic poisons (2-deoxyglucose, dinitrophenol, CN^-) These studies suggest that either Ca^{++} does not enter into these cells normally or that one or more mechanisms which are ordinarily triggered by Ca^{++} are defective in these cells. These studies also underline the importance of ruling out cytotoxicity in ionophore-induced phenomena.

Histamine release from the leukocytes of allergic patients is an accurate *in vitro* index of a patient's allergic state. However, the usefulness of this as a general *in vitro* test for allergy has been limited by the technically complicated histamine assay system and the cumbersome method for preparing leukocytes. An attempt was therefore made to simplify both of these steps and apply the histamine release assay for *in vitro* allergy testing with a battery of common inhalant allergens. The histamine assay system has been automated through the use of Autoanalyzer systems and special extraction methods. Samples are analyzed at the rate of 30 per hour with a sensitivity

of 0.1-0.2 ng. The accuracy and reproducibility of the system are excellent. This automated histamine assay system was then applied for in vitro allergy testing. Nine common pollen and environmental allergens were used at 3 log dilutions for in vitro studies utilizing small volumes of blood (15-20 ml). The clinical evaluation was correlated with the results of the histamine release. Two different procedures have been utilized; the first is the commonly used histamine release from washed leuckoytes. There was excellent correlation between the clinical evaluation and the results of histamine release from washed leukocytes in 17 different individuals. The second method utilized whole heparinized blood; besides the advantage of time saved, the use of blood retains the plasma and might better reflect the immunological reaction which occurs in vivo. Aliquots of blood and allergen are incubated for 1 hour at 37°C; supernatant is then analyzed for histamine release. In 29 individuals tested by both whole blood and washed leukocytes there was excellent correlation between the two tests. There was also good correlation between the clinical evaluation of the patients and the in vitro tests. The precision, accuracy and sensitivity of the automated histamine assay makes feasible its routine application in clinical studies.

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Summary Report of the Humoral Immunity Section
Laboratory of Microbiology & Immunology

Both humoral and cellular immune mechanisms can be invoked in the initiation and progression of inflammation. The inflammatory consequences of activation of the humoral immune system, consisting of the immunoglobulins and complement, have been well documented and include the production of vascular permeability changes, the release of vasoactive amines, contraction of smooth muscle, cellular destruction and the directed migration of inflammatory cells. Recent studies have demonstrated that two complement pathways exist and the relative contributions of each of these to various biological phenonema is the subject of current investigation. In addition, lymphocytes and macrophages are capable of elaborating agents which initiate or modulate the processes involved in inflammatory reactions. After appropriate stimulation, immunologically competent cells synthesize and secrete substances with various biological functions such as chemotaxis of inflammatory cells, inhibition of migration of these cells from an involved area, connective tissue destruction, macrophage activation and cytotoxicity. It is becoming increasingly apparent that an interrelationship exists between the cellular and humoral immune systems. Thus, immunoglobulin synthesis occurs via specific activation of a selective lymphocyte population and very recent evidence suggests that certain complement components interact with specific lymphocyte receptors and modulate cellular immunological function.

The research endeavors of the Humoral Immunity Section focus on the mechanisms underlying the induction of inflammation and its progression to a chronic pathological condition as well as the possible therapeutic manipulation of this response. This section is currently exploring the role of immunoglobulins and complement in the direct mediation of inflammation as well as the ability of these humoral factors and other stimulants to induce the synthesis and secretion of mediators from lymphocytes and macrophages.

Investigations are continuing concerning the role of complement in bone resorption. Fetal rat bones in organ cultures are resorbed in the presence of complement sufficient serum. This effect is abrogated if heated (complement deficient) serum or serum from rabbits genetically lacking the sixth component (C6) of complement is incorporated into the culture medium. The addition of functionally purified C6 to the C6 deficient serum restores resorptive activity. This effect is mediated by prostaglandins as demonstrated by the finding that prostaglandin levels are markedly increased in the bone cultures containing complement. The addition of indomethacin, an inhibitor of prostaglandin synthetase, to the bone cultures abolishes both the appearance of prostaglandins in the culture media and the bone resorption. Immune activition of complement at a cell surface initiates this activity in that resorption is markedly enhanced by the addition of immunoglobulins reactive with cell surface antigens, whereas non-cellular related immune complexes are ineffective. The mechanism of this complement dependent prostaglandin synthesis and the cell types involved are the subjects of current study.

Connective tissue destruction can be attributed in part to the enzymatic effects of collagenase. Macrophages stimulated with endotoxin synthesize and secrete this enzyme. This activity resides in the lipid A moiety of the endotoxin. In addition supernatants from lymphocyte cultures stimulated with immune complexes contain a mediator which induces macrophages to synthesize and secrete collagenase.

The recent postulation that the third component of complement (C3) modulates cellular immune responses is currently under investigation. Receptors for C3 and two of its cleavage products, C3b and C3d, have been described on lymphocytes. Our studies demonstrate that a trypsin derived C3 fragment, C3b, stimulates lymphocytes to produce a factor which is chemotactic for macrophages. Native C3 is considerably less active in this regard. This trypsin derived fragment is analagous to the large C3b fragment which becomes bound to immune complexes during complement activation. The small C3a fragment (anaphylatoxin) is inactive in lymphocyte stimulation. These preparations possess only minimal inherent chemotactic activity. The chemotactic lymphokine which is produced following C3b stimulation is of B (bone marrow derived) cell origin. Prolonged trypsin digestion yields the C3 fragment, C3d. In contrast to the results obtained with C3b, this C3d fragment is totally incapable of activating lymphocytes as determined by mediator release. These fragments have been characterized both immunochemically and by their ability to inhibit rosette formation between erythrocyte-antibody-C3b or erythrocyte-antibody-C3d complexes and their specific C3b or C3d receptors on lymphocytes.

In addition to the receptors for C3 and its fragments on B lymphocytes, these cells also bear immunoglobulin receptors for antigen (Ig receptors) and receptors for 7S antibody (Fc receptors). Interaction of immunoglobulins aggregated either by heat or by specific antigen with the Fc receptors results in lymphocyte activation as determined by their release of a chemotactic factor. Lymphocyte stimulation via the Ig receptors is attained by incubation of cells with anti-immunoglobulin. B cells treated with this reagent also release a chemotactic lymphokine. In these latter studies crosslinking of receptors was a prerequisite for lymphocyte activation in that monovalent Fab fragments were inactive.

The possibility that C3 may constitute one of two signals required for lymphocyte transformation is also being explored. Immune complexes carrying C3b or soluble C3b are incapable of initiating a lymphoproliferative response as determined by tritiated thymidine incorporation. Numerous agents have been assayed both for their mitogenic potential and their complement activating properties. Analysis of the data demonstrates a total lack of correlation between these two biological parameters.

Numerous immunological reactions, both humoral and cellular in nature, have been attributed to endotoxin. Biologically active complement fragments are produced as a result of its ability to activate the alternate complement pathway. The factors involved in the initiation of activation of the alternate complement pathway by endotoxin remain inadequately defined and studies are continuing in regard to a requirement for antibody in complement activation by this agent.

The relative effectiveness of the classical and alternate complement pathways in the lysis of viral infected cells treated with anti-viral antibody and antibody dependent neutralization of herpes simplex virus is under investigation. The contribution of the classical pathway is assessed in the presence of normal guinea pig serum and undigested guinea pig gamma-2 anti-herpes antibody as the respective complement and immunoglobulin sources while that of the alternate pathway utilizes complement lacking the fourth component and gamma-2 $F(ab')_2$ fragments, neither of which support the classical pathway. Whereas lysis of viral infected cells occurs via the classical pathway the alternate complement pathway is markedly inefficient in this regard. The classical pathway also effectively neutralizes antibody coated virus. The alternate pathway can enhance viral neutralization although only at relatively high complement and antibody concentrations.

Steroid therapy is an effective means of combating inflammatory responses. The understanding of the basic mechanisms involved in the effectiveness of these agents has been furthered by the examination of steroid effects on the production of a cellular derived factor which is chemotactic for macrophages. Whereas hydrocortisone has no direct effect on the responding macrophage population, it inhibits the ability of stimulated lymphocytes to produce this chemotactic mediator.

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Summary Report of the Microbiology Section
Laboratory of Microbiology & Immunology, NIDR

The specific projects that make up the research program of the Microbiology Section are summarized under three broad categorical areas.

Taxonomy and Ecology of Microorganisms

An obvious prerequisite for studying microorganisms that comprise any ecosystem is the establishment of reliable means for their identification and characterization. One major project relating to this problem involved a complete updating of the comparative descriptions of taxonomic groups of gram positive, non-sporeforming rods. This extensive undertaking, which actually spanned several years, is now completed. It culminated in a series of manuscripts describing relationships of a number of families, genera, and the species included therein which now appear in the 8th Edition of Bergey's Manual of Determinative Microbiology. This project has been terminated due to the retirement of the senior investigator, M. Rogosa.

Another project within this category was undertaken in collaboration with Dr. Cherry and coworkers at the Communicable Disease Center in Georgia. It involved the development and evaluation of fluorescent antibody conjugates for use in the identification of certain microorganisms present in dental plaque. Protocols were developed and are now available for the production of specific fluorescent antibody conjugates for several species and diverse serotypes of oral actinomycetes. Conjugates have also been prepared and are currently being evaluated for Arachnia propionica serotypes 1 and 2 and for Rothia dentocariosa. It is anticipated that these antibody conjugates will be of value in ecological and epidemiological studies and will also be useful for assessing the therapeutic value of chemical and mechanical plaque-removing programs. This study has also been terminated due to the recent resignation of the senior investigator, Dr. G. Hageage.

Complementing these more classical approaches to microbial taxonomy is a project whose goal is to define actual phylogenetic relationships among microorganisms and, further, to resolve the evolutionary processes that lead to the ability of certain streptococci and lactobacilli to colonize specific econiches within the oral cavity. The fructose-1, 6-diphosphate (FDP) aldolases from Streptococcus faecalis and Pediococcus cerevisiae were purified to homogeneity and used as reference antigens for the preparation of aldolase-specific antisera in rabbits. Employing quantitative serological techniques, the degree of structural similarity was then determined among the aldolases found in representatives of nine genera of lactic acid bacteria. Results from these studies were used to prepare phenetic relatedness maps which reflect natural relationships among 60 species of bacteria belonging to the nine genera studied. This study has also provided some insight into the evolution of the FDP aldolase

itself. Five molecular weight classes of the enzyme were found among the various bacteria surveyed and these five forms appear to reflect differences in the quaternary arrangement of a single conserved subunit. Structural studies of the three most prevelant forms, m.w. 56,000, 121,000 and 176,000, revealed that the smallest aldolase is composed of two - 28,000 molecular weight subunits while the larger enzymes are comprised of four and six - 29,500 molecular weight subunits, respectively. The four subunit aldolase, found almost exclusively among lactobacilli, exhibited the greatest degree of immunological diversity and thus, is probably the ancestral form of the enzyme. In contrast, the six subunit aldolase appears to be the most recent form by virtue of its relatively high degree of antigenic similarity. The two remaining forms of the enzyme appear to be composed of odd numbered subunits and are restricted to only a few species.

Microbial Colonization of the Oral Cavity

It is widely accepted that extracellular glucans produced by S. mutans are involved both in the adhesive interactions among these organisms and in their colonization of the tooth surface. The mechanisms by which these extracellular polysaccharides are synthesized and the nature of their chemical structure, therefore, is being actively studied. The constitutive extracellular glucan synthesizing system (glucosyltransferase) of S. mutans has been extensively purified from cell-free growth medium. The enzyme is a glycoprotein which contains carbohydrate of as yet unknown composition. At least a portion of the carbohydrate moiety is required for catalytic activity, for its partial removal resulted in an irreversible inactivation of the enzyme. The partially purified preparation was further resolved into two major components. One component produced water insoluble glucans from sucrose while the other produced water soluble glucans from sucrose. Electrophoretic studies revealed that the two major components are in turn composed of several protein species, each of which is catalytically active. The feasibility of using this purified glucosyltransferase preparation to immunize sub-human primates against dental caries is now being tested.

In a related study, a number of mutants of S. mutans were isolated which produced extracellular polysaccharides that differed from those produced by the wild type. One of these mutants produced an extracellular enzyme system that synthesized primarily a water soluble glucan from sucrose. Enzymatic and chemical analyses of the products formed by both wild type and mutant revealed little difference between the two with respect to the types of glucosidic linkages. The reason for the solubility of the mutant product is, therefore, unresolved at present. The glucosytransferases from wild type and mutant have also been compared by polyacrylamide gel ectrophoresis. Although the observed patterns were complex, it appears that one or possibly two bands were missing in the mutant.

A third project within this categorical area deals with the formation of an unusual glucose polymer whose physical properties are quite different from the glucans just described. The addition of dextran plus sucrose to cell-free culture supernatants of S. mutans resulted in the formation

of a semi-solid gel closely resembling 2% agar. This phenomenon is dependent upon an extracellular factor(s) present in the culture supernatant fluid, which is referred to as "gel factor" (GF). The factor is produced by cells grown in complex medium with glucose, maltose, or fructose as the primary energy source. GF appears to be a protein; it is heat labile and is inactivated by trypsin. The factor is produced by S. mutans strains belonging to Bratthall's group "d" but not by strains belonging to groups "a", "b", or "c". The potential role of this factor and the gel product in colonization and cell adhesion is being assessed.

Microbial Metabolism and its Regulation

The means by which various oral microorganisms hydrolyze sucrose was long held to be by the action of glucosyltransferase and/or fructosyltransferase. It is now established that in S. mutans, S. sanguis, and S. salivarius, invertase is the major enzyme responsible for providing the cell with monosaccharides from sucrose for growth. This enzyme has been studied in some detail. Several strains of S. mutans produce both extracellular and intracellular invertases. The two forms of the enzyme differ with respect to their molecular weight, K_{ms} for sucrose, and response to the growth substrate. S. mutans was also shown to possess high intracellular levels of glucokinase and fructokinase activity. With this complement of intracellular enzymes the organism has the potential to convert sucrose to phospharylated glycolytic intermediates without prior external hydrolysis and subsequent transport of the monosaccharides into the cell. This project is being expanded to include a study of extrachromosomal DNA in oral streptococci. The possibility that the structural genes which code for one or more of the foregoing enzymes are carried on extrachromosomal elements will be examined. It will also be of future interest to access the possible role of bacterial plasmids in coding for phenotypic traits associated with the pathogenic potential of a given organism.

The ability to ferment mannitol and sorbitol are phenotypic characteristics widely used to distinguish S. mutans from other oral streptococci. The means by which these hexitols are transported into the cell is under investigation. It has been found that mannitol transport in S. mutans is accomplished by a multicomponent phosphoenolpyruvate (PEP) phosphotransferase system. In this system, a soluble, constitutive enzyme catalyzes the transfer of phosphate from PEP to a low molecular weight, heat stable protein (HPr). Neither adenosine triphosphate nor other nucleoside triphosphates would substitute for PEP as a phosphate donor. A second enzyme, which is associated with the cell membrane, then mediates the transfer of phosphate from HPr to mannitol to yield mannitol-1-phosphate. The membrane bound enzyme was inducible and specific for mannitol. This transport system was present in representative strains of all S. mutans serotypes. During the course of this study, several mutants of S. mutans 6715 were isolated which had lost the ability to grow on mannitol. Two of the mutans (mtl^- 208 and mtl^- 113) were found to undergo increased cellular aggregation in the presence of low levels of sucrose when compared with the parental strain. This aggregation was reversed by both dextranase and antibody directed against glucosyltransferase.

Studies of the glucans produced by these mutants revealed a marked decrease in their capacity to synthesize extracellular, water-soluble glucan. Future studies will be directed toward a more complete characterization of the cellular aggregation phenomenon and a precise localization of the biochemical lesion which prevents growth on mannitol.

A great many microorganisms have the capacity to degrade a given substrate by more than one metabolic pathway. The means by which an organism regulates the distribution of substrate carbon among such multiple catabolic pathways is the subject of study for another project within this category. S. faecalis metabolizes glucose more or less exclusively via the Embden-Meyerhof pathway in spite of the fact that the organism has high constitutive levels of the hexosemonophosphate pathway enzymes. This preferential channelling of glucose carbon through the Embden-Meyerhoff pathway is accomplished by the specific interaction of fructose-1, 6-diphosphate (FDP) with a key enzyme from each of the two pathways, which results in differential alterations of their catalytic activity. The Embden-Meyerhof pathway enzyme, lactate dehydrogenase, is completely dependent upon FDP for activity, whereas the hexosemonophosphate pathway enzyme, 6-phosphogluconate dehydrogenase, is strongly inhibited by FDP. In each of these cases, FDP interacts with the enzyme at a site distinct from its catalytic site. The ligand then exerts its modulating effect by mediating a conformational change that alters the affinity of the enzyme for its substrate. These studies on the regulation of carbohydrate catabolic pathways are being expanded to include several species of Actinomyces.

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Report of the Laboratory of Oral Medicine
National Institute of Dental Research
Summary Statement

This is the second annual report of the Laboratory of Oral Medicine (LOM). LOM was created in spring of 1973 to study the etiology and pathogenesis of diseases of the soft tissue of the oral cavity with emphasis on 1) herpes simplex virus; 2) aphthous ulcers and other dermatologic disorders; 3) exocrine and endocrine diseases; and 4) malignant and pre-malignant lesions of the oral cavity. The research program is highly interdisciplinary and organized around disease entities with a strong basic research component and a clinical arm.

In the original plan for LOM, it was estimated that it would take at least two years to make the program operational. Phase I, the reorganization phase, was completed in the fall of 1973. During that period, the organizational plans were formulated and NIDR personnel reassigned to the new Laboratory. It was anticipated that Phase II, the developmental phase, would be completed in 1975. Over the last 12 months personnel in the Laboratory were retrained, new investigators were hired, and the staff moved into its permanent quarters that were specifically designed for the program needs of LOM. With the addition of the new personnel who will be joining LOM over the next several months, the Laboratory will have investigators with training and experience in a number of different disciplines including virology, immunology, cell biology, pathology, electron microscopy, neurology, clinical medicine and clinical dentistry. These individuals will form the nucleus of the interdisciplinary program.

Taking advantage of the new talent and organizational structure of LOM, several new projects requiring an interdisciplinary approach were initiated over the last 12 months. These projects include 1) a double-blind clinical study on the treatment of aphthous ulcers; 2) efforts to isolate viruses from various oral diseases such as aphthous ulcers, Behcet's syndrome and Sjögren's syndrome; 3) quantitative studies on the shedding of herpes simplex virus (HSV) from the lesions of patients with recurrent herpes labialis; 4) investigation of factors responsible for the persistence and reactivation of HSV in the sensory and autonomic ganglia; 5) studies on the efficacy of immunization against the development of latent HSV infection in local sensory ganglia; and 6) use of isoamylase patterns in the serum as a means of detecting and differentiating pancreatic from salivary gland disease.

As indicated last year, we had hopes of initiating a program in oral oncology with emphasis on salivary gland tumors. However, this was contingent upon the availability of clinical material and properly trained personnel. Thus far it has not been possible to get this program off the ground. It has become increasingly clear that a meaningful thrust in this area will require additional personnel. Nonetheless, it is hoped that once the laboratory becomes more fully integrated, it will be possible to initiate at least a segment of this program.

Despite the embryonic nature of the new laboratory and the disruption caused by moving, the staff has been productive in terms of quality and quantity of scientific publications (see bibliography). In addition, the Laboratory sponsored a three day workshop entitled "Viral Immunology and Immunopathology" with thirty internationally known experts in attendance. The proceedings of this meeting will be published as a book by Academic Press.

Probably the greatest advances over the last 12 months came from our projects on the persistence of HSV in local sensory ganglia and the induction of diabetes mellitus by a virus. By using the animal model which we set up in our laboratory last year for studying the latency of HSV in local sensory ganglia, we have gained new information and insight into the feasibility of preventing the development of a latent ganglionic infection by immunization. We found that immunization of mice with HSV-1 protected 95% of the animals against the development of a latent ganglionic infection following inoculation of the lips with homologous virus. Similarly, substantial, but not complete, protection was observed following inoculation of HSV-1 into the cornea, skin, and vagina of immunized mice. Moreover, in up to 30% of the animals, a latent ganglionic infection developed despite the presence of high levels of neutralizing antibody. Why protection was incomplete is not clear, but we believe that it is related to the degree of epithelial injury at the time of exposure of the immunized host to the virus. Once the virus reaches the nerve ending and enters the neuron, it is no longer accessible to antibody. Thus, the virus must be neutralized before it reaches the neuron. In cases where there is a great deal of tissue injury and exudation of serum at the site of inoculation, antibody would be present and could neutralize the virus before the virus reaches the neuron. However, in cases where there is only mild tissue injury and little exudation of serum, virus could reach the nerve endings before it is neutralized and protection would not occur. This suggests that a vaccine which is capable of eliciting high levels of neutralizing antibody nonetheless may not be completely effective in preventing the development of a latent ganglionic infection. The more important factor may be the degree of epithelial injury at the time of viral contact with the host. This hypothesis is presently under study.

New insight also has been gained into factors leading to the development of viral induced diabetes. It long has been suspected that genetic factors play a role in the initiation of diabetes in man. Over the last year we have shown that there is a genetic basis for the development of diabetes in our viral infected animals. Nineteen inbred strains of mice were infected with the M variant of encephalomyocarditis (EMC) virus. We found that these strains could be divided into three groups based on the severity of diabetes. Strains in Group 1 were hyperglycemic and had abnormal glucose tolerance tests; strains in Group 2 had abnormal glucose tolerance tests but were not hyperglycemic; and strains in Group 3 showed neither abnormality. Studies of the F1 hybrids showed that the development of diabetes was inherited as a recessive trait. Over the last couple of months we have succeeded in obtaining purified preparations of beta cells. It should now be possible to study <u>in vitro</u> the ability of viruses to infect, replicate and damage beta cells from the different inbred strains

of mice. These animal studies raise the possibility that in man the susceptibility of beta cells to viral infections also may be genetically determined.

A more detailed description of individual projects follow.

Herpes Simplex Virus

A) Latency of HSV in Sensory Ganglion - Prevention by Immunization: The recurrent epithelial eruptions caused by HSV represent a common affliction and one which may be a source of considerable morbidity. Clinically, HSV type 1 (HSV-1) produces the typical fever blister or cold sore in millions of people, as well as herpetic keratitis which is a leading cause of corneal disease and, in some cases, produces blindness. In addition, the virus can produce encephalitis with severe neurologic sequelae and death. HSV type 2 (HSV-2) is the cause of genital herpes and is perhaps the second most common venereal disease in the United States. Recently, HSV-2 has been linked on a seroepidemiologic basis to carcinoma of the cervix.

Unfortunately, currently available modes of therapy are inadequate for the treatment of most forms of herpes. Therefore, a vaccine which would effectively prevent the infection would represent a major advance. However, in considering the development of such a vaccine, it is necessary to take into account the unusual features of herpetic disease and, in particular, the capacity of the virus to establish a latent infection in sensory ganglia of the nervous system. It has been suspected for some time that the recurrent manifestations of HSV do not result from repeated reinfection but rather from reactivation of endogenous virus which remains latent within the host and is periodically activated to replicate and thus give rise to epithelial lesions. On the basis of a number of clinical and experimental observations, it was theorized that the reservoir for this latent virus is within the cells of the sensory ganglia. Until recently, however, proof for this hypothesis was indirect.

A major breakthrough in confirming this hypothesis came when it was shown that in animals experimentally infected with HSV in the lips, corenea, skin, footpad, or vagina, virus could be detected for prolonged periods in the sensory ganglia innervating the sites of inoculation. The ability to recover virus depended upon the use of explantation techniques whereby the ganglia are placed in culture along with cells known to be sensitive to HSV. By this technique HSV has also been recovered from the trigeminal and dorsal root ganglia of patients.

These findings suggest that sensory ganglia play a critical role in the pathogenesis of herpetic disease; in fact, epithelial eruptions may be considered a secondary manifestation of infection of these ganglia. Thus, when considering the possible role of a vaccine in herpetic disease, it is necessary to know whether or not ganglionic infection can be prevented. Because previous studies involving the efficiency of immunity against HSV focused on prevention of mortality, we embarked upon studies designed to determine whether or not immunization would prevent ganglionic infections.

Our earlier studies demonstrated that inoculation of a variety of epithelial surfaces (i.e. cornea, lip, skin of thigh, footpad and vagina) with either HSV-1 or HSV-2 resulted in development of a local ganglionic infection. The virus appeared to spread from the site of inoculation via the sensory nerves to the ganglia innervating the area inoculated. The ganglionic infection could be divided into an acute and latent phase. During the acute phase, virus could be detected in ganglia for up to two weeks by either homogenizing or explanting the ganglia. However, during the latent phase, which probably persists for the duration of the animal's life, only explants were positive; virus was never detected by homogenization.

Having established this model system, we then went on to test the effect of immunization upon the acquisition of a ganglionic infection. Mice first were immunized by three or more intraperitoneal injections of live virus. Having determined that this immunization procedure itself did not result in a latent infection of the ganglia to be assayed (i.e. the trigeminal and lumbosacral dorsal root ganglia) we then went on to challenge mice with virus by different epithelial routes. Animals to be challenged with HSV-1 were immunized with HSV-1, while animals to be challenged with HSV-2 were immunized with HSV-2.

The results of these studies revealed that both the route of inoculation as well as the virus subtype influenced whether or not ganglionic infections developed in immunized animals. With HSV-1 a difference in the degree of protection against ganglionic infection was noted following inoculation by the different routes. In mice challenged by the footpad route, no protection was seen, while in mice challenged by the lip, corneal, vaginal and skin routes, 74-96% protection was observed.

In contrast to the protective effects seen with HSV-1, animals immunized with HSV-2 and challenged with HSV-2 by the corneal, footpad and vaginal routes showed little, if any, protection.

The role of neutralizing antibody in conferring protection was next examined. Mice were bled after immunization, but before viral challenge by the various epithelial routes. Antibody titers in immunized mice that subsequently developed a ganglionic infection then were compared with those that did not develop a ganglionic infection; no significant difference was found between the positive and negative groups. Furthermore, it was noted that ganglionic infection often took place despite the presence of high levels of antibody (neutralization titers of 512 or greater).

What, then, is the explanation for the differences in protection, especially when animals are challenged by different routes? We suspect that the variation in susceptibility may be related to the degree and depth of tissue injury at the time of viral contact. Each area was abraded as part of the inoculation procedure; in the case of the lip, thigh, cornea and vagina, the epithelial surfaces are fragile and the abrasion led to considerable injury accompanied by exudation of serum. Thus serum and/or immune cells would have the opportunity to neutralize or inactivate the inoculum before the virus adsorbed to nerve endings. In contrast, the footpad surface is thick and abrasion led to relatively little exudation

of serum. The virus, therefore, could bypass the immune system by adsorbing to nerve endings before neutralization occurred; once virus enters the cytoplasm of the nerve terminals, it is no longer vulnerable to immune defense mechanisms. This formulation of events at the epithelial surface is currently being tested by ongoing studies involving the effect of graded injury upon development of ganglionic infection.

The reason for the greater protection afforded against HSV-1, as compared to HSV-2, remains to be explained. Possibly differences in the kinetics of neutralization or differences in the "gangliatropism" of the two viral subtypes may be responsible. On the other hand, these findings may reflect fortuitous differences in our laboratory strains of HSV which are not necessarily intrinsic to the two viral subtypes. We are presently engaged in studies employing a variety of prototype strains as well as virulent and avirulent substrains in order to clarify this issue.

What are the implications of these studies for the development of a vaccine against HSV in man? They point out that a number of biological problems must be overcome before a vaccine can be judged successful. Not only may inactivated HSV be oncogenic, as has been suggested by others, but live virus used for immunization purposes could itself induce a latent ganglionic infection. In addition, our studies indicate that under some circumstances, immunization may not protect the host and a certain degree of "breakthrough" can occur. Before generalizations can be made, however, it will be necessary to carry out similar studies in other animal species using other viral strains. An additional obstacle in evaluating the effectiveness of a vaccine is our still poor understanding of how man is naturally infected. Further studies are needed in this area. The experiments performed over the last year, however, represent an important step in coming to grips with the issue of immunization against HSV, for it is the ganglionic infection which is central to the pathogenesis of recurrent disease.

Studies also were undertaken to investigate the role of immune mechanisms in reactivation of latent virus. It has been proposed (although not generally accepted) that reactivation of HSV might represent a defect in immune defenses. We previously showed that sciatic neurectomy provides a highly reproducible means of reactivating virus in lumbosacral dorsal root ganglia. When mice harboring latent virus in these ganglia were subjected to neurectomy, virus once again could be recovered in the ganglionic homogenate, i.e. the virus was reactivated. To see if reactivation could take place in the presence of immunity, latently infected, highly immunized mice with serum neutralization titers of 1024 were neurectomized, and three days later the mice were sacrificed and ganglia homogenized. In both non-immunized (control) and immunized (experimental) mice, 25% of the latently infected animals exhibited viral reactivation. This study supports the contention that reactivation is not due to a lapse in immune defenses, but more likely is related to still undetermined alterations in the cells of the sensory ganglia. Such alterations may be initiated by nerve injury, changes in nerve impulses or modifications of the extracellular milieu. Future studies will be directed towards elucidating the factors responsible for reactivation.

B) Cell Mediated Immunity in HSV Infection: The immunological defense against HSV may be analyzed at two levels: 1) immune factors which prevent the development of a latent ganglionic infection (described above) and 2) immune factors which control the recurrent epithelial lesions in the already infected host. Evidence for the importance of cell-mediated immunity in controlling the recurrent episodes of HSV infections in man comes mainly from observations on the congenital immunodeficiency syndromes. Patients with Bruton's agammaglobulinemia have normal cell-mediated immunity; they have recurrent infections by pyogenic pathogens but are not abnormally susceptible to HSV infections. However, congenital conditions in which cell-mediated immunity defects are prominent (e.g. Wiscott-Aldrich syndrome) result in a high susceptibility to recurring and often fatal HSV infections. Cancer chemotherapy and immunosuppressive therapy, which depress cell-mediated immunity, also lead to increased viral infections.

Animal studies of HSV infection, particularly regarding the role of cell-mediated immunity, have been limited. Increased morbidity and mortality due to HSV infection occur in mice treated with anti-lymphocyte sera and immune spleen cells transferred to normal mice can confer immunity. In none of these experiments, however, were the relative roles of humoral (antibody) and cell-mediated immunity (primarily T lymphocytes) to HSV established. Experiments to define the roles of the various effector limbs of the immune response were therefore begun. The plan was to make mice deficient in both the humoral and cell-mediated responses, leaving the animals highly susceptible to HSV infection. Attempts then were made to reconstitute resistance by inoculating the animals with anti-HSV antibody or defined populations of normal or immune lymphocytes.

Mice were made deficient in all immune responses by a combination of adult thymectomy, lethal irradiation followed by bone marrow transplants, and subsequent treatment with anti-thymocyte sera. Such (TXBM) mice are devoid of T lymphocytes, as shown by the inability of their spleen cells to mediate graft-vs-host reactions, supply helper T lymphocyte functions, or react to T lymphocyte mitogens. In the absence of T lymphocytes, their B lymphocytes are unable to differentiate into plasma cells producing anti-HSV antibody. Such mice are 1000-fold more susceptible to intraperitoneal HSV infection than normal mice. Large doses of immune sera given up to 48 hours after infection afford some protection, but the biological significance of this finding is unclear since the amount of antibody required is much greater than would be found in normal mice at that time after infection. Resistance to infection was partially restored when 25 million normal spleen cells were inoculated into TXBM mice 24 hours prior to HSV infection, and 75 million normal spleen cells resulted in near maximal restoration of resistance. Immune spleen cells (taken 12 days after infection of the donor) are much more efficient than non-immune spleen cells, with only one-third to one-fifth as many immune spleen cells as non-immune spleen cells required for an equivalent amount of protection. Using appropriate methods to separate T lymphocytes from B lymphocytes, we have shown that it is the T lymphocytes that are required for protection.

Another series of experiments was completed which demonstrate that cell-mediated immunity is of greater importance than humoral immunity in

recovery from HSV infection. Mice were treated from birth with goat anti-sera directed against the heavy chain of mouse IgM immunoglobulin. This anti-sera eliminates or prevents the normal development of B lymphocytes, which contain immunoglobulin on their cell membranes. At six weeks of age, these mice were found to have no demonstrable B lymphocytes in their spleens by immunofluorescent studies and by the inability of their spleen cells to respond to B lymphocyte mitogens. In particular, they were incapable of producing antibody to HSV. However, their T lymphocyte functions and cell-mediated immunity were intact and they were almost as resistant to HSV infection as normal mice. This experiment speaks against a necessary role for antibody in recovery from HSV infection, although antibody may be helpful in limiting the dissemination of virus. It also suggests that antibody-dependent lymphocytotoxicity, a phenomenon reported to occur in vitro against HSV-infected cells, is not necessary for recovery since no detectable IgG antibody to HSV was produced in these mice.

A number of T lymphocyte subpopulations are now known and at present, experiments are in progress to define more specifically the T lymphocytes primarily involved in conferring resistance to HSV infections in mice.

C) Interferon as a Mediator of Cellular Immunity in HSV Infection:
Studies in our laboratory over the last couple of years showed that the hosts' immunological defense against HSV can be divided into an immunologically specific antigen recognition phase and a non-specific effector phase. In the first phase, antiviral antibody, complement and immune lymphocytes react with free virus or viral antigens on the surface of infected cells. This results in cell lysis and neutralization of extracellular virus. However, the spread of the virus is not stopped because immunologically mediated lysis occurs after the virus has already spread to contiguous cells. This suggested that the non-specific phase of the defense, that is the release of lymphokines, particularly interferon, from immunologically stimulated lymphocytes, might be required for finally halting the spread of the infection.

During the past twelve months we have extended our studies on the role of immunologically induced interferon in stopping the spread of HSV. When HSV is incubated with normal rabbit kidney cells or lymphocytes from unimmunized animals, little interferon is produced. However, HSV produces high levels of interferon when incubated with lymphocytes from HSV-immune rabbits. Immunologically-specific induction of interferon has the theoretical advantage of enabling the immune host to produce interferon in response to a variety of structural and nonstructural viral antigens, to which the non-immune host would not be able to respond.

Since it is known that certain viruses replicate in lymphocytes, especially dividing lymphocytes, this potentially important host defense mechanism might be suppressed if the virus infects and destroys lymphocytes. The neutralization of infectious virus by antibody would prevent the destruction of lymphocytes, but the covering of antigenic sites on the virion by antibody might prevent the virus from stimulating immune lymphocytes to produce interferon. To study this possibility, we prepared virus-antibody complexes, using amounts of antibody that were sufficient to reduce viral

infectivity by over 99.99%. Nonetheless, these virus-antibody complexes when incubated with immune lymphocytes were capable of inducing interferon. It appears that the host has developed an effective way of protecting the cells of the immune system from destruction by neutralizing the infectious virus, while at the same time, allowing the virus or viral antigens to stimulate immune lymphocytes to produce interferon.

Aphthous Ulcers and Other Dermatologic Disorders

This area of research was initiated last year and includes virologic, immunologic and diagnostic studies into the etiology of aphthous ulcers, Behcet's syndrome, Sjögren's syndrome, and other related disorders. Recurrent aphthous ulcers are characterized by mucosal lesions of the lips, cheeks, tongue, palate, gingiva, and pharynx. In addition, mucosal areas of the genital and anal surfaces may be involved. Behcet's syndrome consists of recurrent oral and genital ulcers, iritis, retinitis, arthritis, skin lesions, GI lesions, and central nervous system involvement. Some people believe it is part of the aphthous spectrum, representing the most extreme form. Sjögren's syndrome is characterized by an inflammatory infiltrate of the salivary glands and the patients suffer from dryness of the mouth.

Despite the frequency and severity of these three disorders, very few attempts have been made to isolate viruses. Over the last year, we have obtained serum and biopsies from patients with these diseases, and have attempted to isolate virus. To date, we have examined specimens from 21 patients with aphthous ulcers, 4 patients with Behcet's syndrome, and 6 patients with Sjögren's syndrome. Each biopsy was divided into three parts; one part was fixed in formalin for histopathology, another part in gluteraldehyde for electron microscopy and a third part was explanted and grown in vitro. Some explants have been in culture for 12 months and are in their 20th subculture. Various specimens also have been inoculated into primary and continuous cell lines and blind-passaged two to three times. In addition, a variety of other techniques have been used to isolate and identify viruses. Thus far, viruses have not been isolated from those specimens and virus-like particles have not been detected by electron microscopy. A transient cytopathic effect, however, has occasionally been observed, but the phenomenon is difficult to reproduce. Whether the cytopathology is due to a still undetected virus, or to other factors, remains to be determined.

In addition, attempts have been made to identify unique antigens in cell cultures prepared from these diseases. Patient sera and sera prepared against a number of common viruses were used as antibody sources. By several techniques, including complement fixation, immunofluorescence and complement mediated cytotoxicity, we have been unable to demonstrate unique antigens.

Our failure, thus far, to isolate an infectious agent or a unique antigen does not rule out a viral etiology. First, infectious virus may not have been present at the time that most of our biopsies were obtained. Attempts will now be made to obtain tissue at a much earlier stage in the course of the disease. Second, a more vigorous effort will be made to look for,

and activate, latent viruses.

Diseases of the Endocrine and Exocrine Glands

Several lines of evidence suggest that viruses may be one of the factors that contribute to the development of diabetes. For over 75 years physicians have noticed a close temporal relationship between mumps parotitis and the onset of juvenile diabetes. However, a causal relationship has not been established. An animal model of mumps pancreatitis would be very helpful in interpreting the studies in humans. Extensive investigations in our laboratory with mumps virus, thus far, have been unsuccessful in producing a pancreatic infection in mice, guinea pigs, or hamsters. Coxsackie viruses, on the other hand, readily infect the pancreas of mice. Based on studies with 22 different Coxsackie B virus isolates, we have found that these viruses are remarkably virulent to the acinar cells of the pancreas but do not damage the beta cells or produce diabetes.

Earlier studies from our laboratory suggested that development of encephalomyocarditis (EMC) viral induced diabetes was genetically determined. Over the last year, we have investigated this possibility in depth. Nineteen inbred strains of male mice were infected with EMC virus. Five strains became hyperglycemic and had abnormal values in glucose tolerance tests; three strains remained normoglycemic but had abnormal values in glucose tolerance tests; and the remaining eleven strains showed no abnormalities in blood glucose levels or glucose tolerance tests. Female mice from three of the strains tested also developed hyperglycemia, but in one strain (DBA/2) the hyperglycemia was less severe in females than in males. Other experiments showed that castrated DBA/2 males developed less severe hyperglycemia than uncastrated males, even though the degree of damage to beta cells appeared to be similar in the two groups. It was concluded that host factors influence both the development and expression of viral induced diabetes mellitus.

To further study the genetics of viral induced diabetes, susceptible strains of mice were bred with resistant strains of mice. C57/BL mice do not develop diabetes when infected with EMC virus even though the mice become quite ill, and many die of myocarditis. In contrast, most SWR mice survive the acute infection, but two-thirds of the animals develop signs of diabetes. When the F1 hybrids were infected with EMC virus, we found that only a few of these animals had glucose values outside the normal range. Thus it appears that susceptibility to the diabetogenic effect of EMC virus is inherited as a recessive trait, although the F1 hybrids are intermediate in their phenotype. When the F2 generation was infected with EMC virus, a small fraction (6%) of the mice became severely diabetic, but a much larger fraction had glucose values well outside the normal range. A clearer definition of the number of genes involved will require more data from the F2 generation and from appropriate backcrosses. These experiments are currently underway.

The conclusions drawn from crossing SWR and C57/BL mice are supported by different combinations of susceptible and resistant mice. When DBA/2 mice

were bred with C57/BL mice, the gene(s) controlling susceptibility to the diabetogenic effect of EMC virus also was found to be recessive. Similarly, both AKR and C3H/He mice were resistant to the diabetogenic effect of EMC virus; the cross of these mice with DBA/2 mice resulted in an F1 hybrid which was resistant to the diabetogenic effect of EMC virus.

A different approach to the genetic control of viral induced diabetes is to study hybrids resulting from the mating of two susceptible strains of mice. If the locus controlling viral induced diabetes in the two strains is the same, then the F1 and F2 generations should maintain a degree of susceptibility similar to the parents. On the other hand, if different loci are involved, then at the F1 generation, one might observe resistance (or increased susceptibility) due to the heterozygous state at more than one locus. At the F2 generation, one might see segregation of genes that would confer either resistance or increased susceptibility. Inbred DBA/2 and SWR mice do not share any common heritage, and as such provide an opportunity to test this hypothesis. These studies are now in progress.

Over the last year, we also have attempted to develop an in vitro system for investigating the relationship between viral replication and alterations in beta cell function. A method was worked out for isolating relatively purified preparations of beta cells by use of collagenase and a preformed Ficoll gradient. By this method, beta cells were obtained from SWR mice several days after infection with EMC virus. Light microscopic studies showed that the beta cell preparations contained high concentrations of virus. By immunofluorescence, viral antigens were demonstrated in the degenerating beta cells.

In other experiments, freshly isolated beta cells from uninfected SWR mice were infected in vitro with EMC virus. Degeneration increased linearly with time, reaching 50% at about 48 hours. Uninfected beta cells exhibited relatively intact morphology under the same conditions. Endocrine studies showed that the content of insulin in the infected beta cells began to decline at 24 hours after infection when the viral titer reached its maximum.

When these techniques were applied to C57/BL and to other strains of mice that did not develop overt diabetes, it became apparent that degranulation and degeneration of beta cells was reduced significantly as compared to the susceptible strains, even though virus could replicate in the C57/BL beta cells. This interesting observation is presently under investigation.

Clinical Studies

Salivary Gland Disease: Saliva is the natural occurring solvent contained in the oral cavity and plays a major role in oral health and disease. Without saliva the integrity of the oral cavity is impaired. It is common knowledge that increased tooth decay, loss of taste, difficulties in food ingestion and mucosa disease are consequences of xerostomia. The whole saliva pool consists of contributions from the so-called major (parotid, submandibular, sublingual) and minor (palatal, lingual, labial, retromolar, etc.) salivary glands. These glands

separately and collectively are subject to disease. Composition of the secretions from the different glands varies and reflects to a great degree the histological cell type of the specific gland. The secreting cells of the parotid gland are of the serous type, those of the sublingual gland are of the mucous type, while those of the submandibular gland are a mixture of the two types.

Diseased salivary glands may have a local (e.g., infection, neoplasms, sialolithiasis) or systemic etiology (e.g., Sjö gren's syndrome, sarcoidosis, Kwashiorkor). The exocrine function of the salivary glands is well recognized but its physiological import and diagnostic potential has not yet been fully exploited. The possibility that the salivary glands also may have an endocrine function has received even less attention.

The major protein in human parotid saliva is amylase. It had been thought to be identical to that produced by the pancreas. However, by polyacrylamide gel electrophoresis, it was shown that salivary and pancreatic amylases were not identical; in fact serum amylase can be separated into the pancreatic and salivary forms.

In our laboratory, a technique has recently been developed to quantitate the amounts of pancreatic and salivary amylase in serum. By means of this technique, it was found that infection of mice with Coxsackie B virus produced severe acinar pancreatitis and a pronounced rise in serum amylase levels. Concurrently, the content of amylase in the pancreas fell, and remained less than 5% of normal for several months. Analysis of serum isoamylases by polyacrylamide gel electrophoresis revealed that during the acute phase of the infection, the hyperamylasemia was predominantly pancreatic in origin. Following the acute infection, the amylase level in the serum returned to the normal ranges but isoamylase analysis revealed a marked decrease in the pancreatic form. In contrast, EMC virus produced severe beta cell damage but relatively little damage to the acinar cells of the pancreas or parotid gland. Serum amylase levels rose only slightly during the acute phase of the infection but were depressed for prolonged periods thereafter. Isoamylase analysis revealed decreased levels of both pancreatic and salivary forms. These studies suggest that quantitation of serum isoamylase might be a useful tool for detecting and differentiating pancreatic and salivary disease.

The isoamylase technique has recently been extended to humans with pancreatic and salivary disease. Patients with cystic fibrosis had variations in serum amylase levels that could be totally accounted for on the basis of alterations in pancreatic isoamylase. Salivary isoamylase levels in the serum remained unchanged. Preliminary data suggest that, in some cases, the early stage of the disease is characterized by a hyperamylasemia while later in the course of the disease pancreatic insufficiency may develop with significantly lower levels of pancreatic isoamylase. These observations await confirmation with a larger number of patients.

Sera from patients with Sjögren's syndrome also were studied. In this disease salivary isoamylase levels varied, while pancreatic isoamylase levels remained relatively constant. Significantly higher salivary iso-

amylase levels were found in some patients with Sjögren's syndrome. In many others, however, salivary isoamylase was within the normal range or slightly lower. This investigation will be continued to ascertain the diagnostic utility of this technique and to better understand the significance of variations in serum amylase levels. In addition, sera from patients with salivary and pancreatic carcinoma and acute and chronic pancreatitis will be studied. Attempts also are being made to develop a highly sensitive and quantitative radioimmunoassay to measure pancreatic and salivary isoamylase.

Along a somewhat different line, it was recently reported that in rats, von Ebner's gland, which is at the base of the tongue, produces a lipase. It was previously thought that fat digestion occurred primarily in the gut (below the stomach). We now have evidence of a preduodenal lipase in humans. Efforts are being made to localize the origin of this lipase.

Studies also have been initiated to investigate the effect of pilocarpine on parotid gland secretion in patients with Sjögren's syndrome. Parotid function is being monitored by scintigraphy, sialometry and salivary protein analysis. The possibility exists that by keeping the salivary glands functioning, xerostomia may be ameliorated by preventing pressure atrophy.

Treatment of Aphthous Ulcers: Tetracycline is widely used in the treatment of recurrent aphthous ulcers. However, a carefully controlled objective study has never been performed. To determine the effectiveness of tetracycline in decreasing the severity and frequency of recurrent aphthous ulcers, a double blind study was initiated. The study consists of two phases of patient evaluation. In phase I patients spend eight weeks keeping a daily diary of oral symptoms and signs, and are seen weekly by our clinical staff for a similar evaluation. In phase II each patient again keeps a daily diary and is seen for weekly evaluations for a total of 12 weeks. However, in this phase treatment is administered according to a pre-selected and randomly-assigned code. Patients receive either tetracycline or placebo.

The daily diary is filled out each morning or evening by the patient. He indicates schematically the position of every ulcer; the size is determined by comparison with circles on the diary sheet. In addition, a subjective evaluation of pain (none, slight, moderate, or severe) associated with each ulcer is recorded. Oral temperature and other medication are noted.

The weekly evaluation by the clinical examiner is similar, except that the actual size of each ulcer is measured. In addition, local or systemic manifestations of drug allergy or side effects are recorded. Bi-weekly WBC, differential and ESR are determined; SGOT, BUN and urinalysis are performed monthly.

The study is carried out in a double blind, randomly selected manner. As an acceptable alternative to a cross-over design, the patients are randomized on the basis of data obtained in phase I so that each group

(i.e., tetracycline or placebo) consists of similar characteristics (age, sex, race, frequency and severity of recurrent ulcers).

Each patient in the experimental group takes 250 mgm of tetracycline, q.i.d. for five days, starting on the first day of a clinical attack. Thereafter, he will take no more tetracycline for at least nine days. The drug is given as an oral suspension, swished in the mouth for five minutes, then swallowed. Patients on placebo go through the same procedure.

With this design, each patient in the study will take mouthwash (tetracycline or placebo) for five days. At the completion of phase I and II the frequency, duration and size of the oral ulcers are determined from the daily records. The results for phase I (baseline) and phase II (treatment) are evaluated statistically. As of this date, seven patients have completed phase I and II. Eight other patients are presently in phase I, and two patients are in phase II. Of the seven patients who completed the protocol, four patients received tetracycline and three patients received placebo. No significant difference was found between the treated and untreated patients. The protocol will be continued until a total of 36 patients have been evaluated.

Future plans include investigation of a recent finding that over 95% of the patients with recurrent aphthous ulcers have a low serum folate level. Attempts will be made to verify this observation by use of a more precise method for measuring folate levels.

Shedding of Herpes Simplex Virus from Oral Lesions: A variety of factors including stress, trauma, fever, or excess exposure to sunlight are thought to be capable of reactivating HSV which is latent in the trigeminal ganglion. The reactivated virus travels down the neuron and initiates local labial lesions. Virus can be recovered from the vesicular fluid of these lesions, but little information is available on how much virus is present or how long patients shed virus from open lesions.

Moreover, as indicated earlier, despite the presence of high levels of neutralizing antibody, herpes labialis is characterized by frequent recurrences. In a number of viral infections, the coexistence of antibody with virus results in the formation of infectious virus-antibody (VA) complexes. These complexes are detected *in vitro* by incubating virus isolated from infected animals with complement or antiglobulin sera, and depending on the class of antibody bound to the viral surface, the VA complexes can be neutralized by these serological reagents. In experimental studies, the deposition of VA complex in capillary walls and glomeruli has been associated with marked inflammatory reactions and, in some circumstances, with immune complex glomerulonephritis. Although HSV is known to form infectious VA-complexes *in vitro*, the existence of such complexes in human herpetic lesions has not been demonstrated.

Over the last 12 months, in collaboration with Dr. Charles Daniels at Duke University, we initiated a study to 1) quantitate the amount of virus shed from lesions of patients with recurrent herpes labialis at different times after the onset of the disease, and 2) to demonstrate and quantitate

infectious VA complexes in vesicular fluid. Our studies showed that on the first day, the vesicular fluid contained $10^{5.3}$ plaque-forming units (PFU) of HSV per microliter. By swabbing the surface of the lesions with a sterile pledget, $10^{6.2}$ PFU of virus was isolated from the inflamed labial mucosa. The amount of virus recovered from the labial surface dropped on the second and third day to $10^{5.0}$ and $10^{3.0}$ PFU, respectively. In two patients on immunosuppressive drugs, high concentrations of virus (greater than $10^{4.0}$ PFU) were obtained for three or more weeks. These studies suggest that individuals with active lesions should be regarded as infectious for at least four days after rupture of the vesicle. Patients on immunosuppressive drugs shed virus for considerably longer periods and present an even more serious threat to their fellow patients and medical personnel.

Recent studies in mice showed that by topically applying $10^{6.0}$ PFU of HSV to abraded skin, a latent infection of the ganglion developed in up to 100% of the animals. Under certain circumstances, immunized mice also could be infected. Our studies on vesicular fluid suggest that herpetic lesions contain a sufficient amount of virus to infect abraded skin and that systemic immunity against HSV may not always protect the exposed host from contracting a latent infection.

The presence of infectious VA complexes in herpetic lesions was demonstrated by examining 52 isolates from 28 patients at various times during the course of their disease. Seventy-one percent of the patients had VA complexes in their lesions on the first day of the vesicular eruption, and by the third day, all of the lesions examined contained complexes. It is concluded that in nature, HSV may be transmitted in the form of infectious VA complexes.

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REPORT OF THE
NEUROBIOLOGY AND ANESTHESIOLOGY BRANCH
NATIONAL INSTITUTE OF DENTAL RESEARCH
SUMMARY STATEMENT

The Neurobiology and Anesthesiology Branch was established in FY 1974 as part of the Institutes' research initiative in the area of pain and pain control. This Branch is concerned with the elucidation of basic mechanisms of oral-facial sensation with particular emphasis on pain sensation, and with the assessment and measurement of experimental and clinical pain in humans. Fundamental research on peripheral and central nervous system mechanisms of oral-facial sensation is conducted by the Neural Mechanisms Section which was established in 1968 as a separate Section directly under the Office of the Director of Intramural Research. The primary objective of this research group is to correlate behavioral responses to noxious and non-noxious stimuli in monkey with neuronal structure and function at various levels of the trigeminal system. A multidisciplinary approach is employed and includes the following research activities at present:

(1) electrophysiological studies of the response of single trigeminal nerve fibers and trigeminal brain stem neurons to noxious and innocuous thermal and mechanical stimuli applied to the oral-facial region of monkeys;

(2) neurocytological studies of the receptor, primary afferent and brain stem organization of the trigeminal system in cat and monkey, utilizing light and electron-microscopic techniques;

(3) behavioral studies involving pain and temperature discrimination in monkeys trained to avoid potentially-noxious or noxious stimuli applied to the face; and

(4) measurement and assessment of experimental pain utilizing various psychophysical methods.

The Anesthesiology Section which previously was an inactive component of the Oral Medicine and Surgery Branch, was reestablished as part of the Neurobiology and Anesthesiology Branch. This Section which only recently has recruited personnel, will conduct research on the development and application of new methods of pain control. Present activities include physiological, pharmacological and psychological studies of the effects and efficacy of new pharmacological agents utilized in the control of pain in ambulatory dental patients.

Progress During the Last Year

Behavioral and physiological studies

Our approach to the study of pain mechanisms involves the use of noxious heat stimulation to determine the trigeminal peripheral and central neuronal populations which are involved in transmitting or coding information about the presence of noxious stimuli applied to the monkey's

face. A behavioral animal model has been developed to study escape behavior in monkeys in response to noxious heat stimuli. Escape behavior in monkeys correlates highly with human subjective reports of pain under identical stimulus conditions. The model has the following advantages: (1) A natural stimulus (noxious heat) is utilized; this stimulus is easily quantified and activates a restricted population of peripheral nerve fibers; (2) The paradigm includes positive and negative reinforcement and eliminates the tendency of animals to avoid rather than escape noxious stimuli; (3) The animal's escape performance is sensitive to motivational shifts independent of his sensitivity to the noxious stimulus; and (4) Peripheral and central neural events can be analyzed and correlated with the monkey's behavioral performance.

In the experimental situation, Rhesus monkeys were trained to detect the termination of an innocuous temperature increase and to escape noxious thermal stimuli. Temperature increases at a rate of 10^{o}C/sec were provided by a contact thermode positioned on the face. The monkeys were rewarded with grape juice when a panel switch was released within a fixed time period after the termination of the stimulus. On trials in which the temperature increase reached the noxious heat range (45^{o} to 51^{o}C), the monkey could escape the stimulus by releasing early, but received no reward. Monkeys that received sufficient water in the cage had escape thresholds (probability of early release = 0.5) less than 48^{o}C. The escape threshold was independent of the baseline or adapting temperature over the range of 30^{o} to 37^{o}C. Lip movements associated with noxious heat stimulation were monitored by a sensitive accelerometer attached to the thermode, and consistent with the behavioral results, occurred only at final temperatures of 48^{o}C or higher. Under water-restricted conditions, escape thresholds were greater than 51^{o}C, although lip movements continued to occur at temperatures of 48^{o}C or higher.

These results indicate that escape thresholds in monkeys are dependent on the motivational state of the animal and can be altered independent of any change in the monkey's sensitivity to the noxious thermal stimulus.

We have found that there are only three peripheral nerve fiber populations innervating the monkey's face which are sensitive to temperature changes in the 47^{o}C to 51^{o}C range and are capable of initiating central neuronal activity involved in the monkey's ability to escape from noxious heat stimuli:

(1) Unmyelinated (C) heat nociceptors had thermal thresholds ranging from $38\text{-}49^{o}$C and exhibited maximum sensitivity in the 45^{o} to 52^{o}C range. They were activated by non-noxious, intense mechanical stimuli. A comparison of the mean frequency of discharge of these nociceptive afferents with escape latencies in the behavioral experiments suggests that their activity may contribute to the monkey's ability to escape with shorter latencies during shifts to higher final temperatures.

(2) Finely myelinated (A delta) heat nociceptors were similar to C heat nociceptors, but exhibited higher discharge rates in response to stimuli in the 45^{o} to 52^{o}C range.

(3) Individual warm fibers (A delta and C) were sensitive to temperature changes in the noxious heat range, but few were maximally sensitive to noxious heat stimuli above 47°C, and therefore they alone cannot provide input essential for the monkey's escape behavior.

We conclude that activity in A delta or C heat nociceptors, or both, is essential for escape behavior to noxious heat. However, warm fibers may play a role if central summation is a critical component of such behavior.

Recently we have begun studies to examine the response properties of neurons in the trigeminal brainstem nuclear complex which receive input from the above fiber populations responsive to noxious heat. Neurons within trigeminal nucleus caudalis and subjacent reticular formation were studied in rhesus monkeys anesthetized with chloralose. This analysis yielded five classes of units distinguished by the range of mechanical stimuli over which they responded: (1) touch (19 units), (2) touch-pressure (22 units), (3) touch-pressure-pinch (39 units), (4) pressure-pinch (24 units), and (5) pinch only (17 units). All five classes had axon projections to somatosensory thalamus. Axonal conduction velocities of each class were found to become progressively slower as classes changed from 1 to 5. Receptive field sizes were usually small (1-2 cm^2) for class 4 and 5 cells, and larger for class 3 cells. The marginal layer of N. caudalis contained mostly class 4 and 5 cells but some class 3 cells. The superficial portion of the magnocellular layer contained mostly class 1 and 2 cells, while neurons at the base of this layer contained mostly class 3 cells and some class 4 and 5 cells. Cells in the subjacent reticular formation included all 5 cell classes and showed a tendency to have very large receptive fields. Neurons responding to noxious skin temperatures (44-52°C) included 48 percent of all class 3 units, 21 percent of all class 4 units, and only 6 percent of all class 5 units. No units were found that responded exclusively to thermal stimuli. No class 1 or 2 units responded to thermal stimuli. These studies suggest that there are 2 major populations of neurons (types 3 and 4) in nucleus caudalis responsive to noxious heat. These neurons can be distinguished by location, receptive field size, axonal conduction velocities, and responses to mechanical stimuli. We plan to study further the properties of such neurons in awake rhesus monkeys trained to escape noxious thermal stimuli applied to the face.

In another behavioral paradigm, detection thresholds to warming stimuli have been examined. We have found that reaction times (RTs) to warm stimuli applied to the monkey's face are correlated with parameters of the stimuli and provide an index of warm sensation in non-human primates. A spring-loaded, feedback-controlled, contact thermode (1 cm diam) was applied to the upper hairy lip in water-deprived monkeys. Each monkey was trained to depress a panel for the random period of time (2-8 sec) preceeding the onset of a warming shift. Release of the panel within 2.5 sec from the onset of warming was rewarded by water (0.5 cc). The stimulus parameters investigated were magnitude (0.4° to 10°C), velocity (0.3° to 10°C/sec), adapted temperature of the skin (25°, 30°, 35° and 40°C), and interstimulus interval. RTs were influenced by stimulus magnitude only when the warming shift was small (<1°C) and the stimulus velocity was

fast (≥5°C/sec): larger shifts resulted in shorter average RTs. Otherwise, RTs were determined by the rate of stimulus change regardless of the stimulus magnitude: faster rates resulted in shorter average RTs. At adapted skin temperatures of 30°, 35° and 40°C, average RTs varied inversely with adapting temperature in both monkeys. However when the skin was adapted to 25°C, average RTs were shorter than at higher adapting temperatures for one monkey but longer for the other monkey. This finding suggests that when the adapted temperature of the skin is low, detection of small warming shifts (0.4 to 3.0°C) may be based either on the reduction of activity in cold fibers (first monkey) or a weak onset of activity in warm fibers (second monkey). Finally, for interstimulus intervals <20 sec, average RTS to the second warming shift were longer when the preceeding shift was relatively large (5°C) but were not influenced when preceded by a smaller shift (0.6°C).

These findings indicate that RTs vary with changes in stimulus parameters and that reaction times are a good behavioral measure of sensory performance. Present studies are underway to correlate these behavioral findings with response properties of warm and cold fibers innervating the same facial region in monkeys. We plan to determine which components of the neural discharge of these peripheral fiber populations are critical for the monkey's behavior.

Anatomical Studies

During the past year our anatomical studies have further implicated trigeminal nucleus caudalis as an important site in the trigeminal pain pathway. The objectives of these studies are to examine the synaptic connections of the primary trigeminal axons which arborize in the substantia gelatinosa (SG) layer of the spinal trigeminal nucleus and to identify the interneurons and projection neurons which subserve trigeminal pain-temperature pathways. Electron microscopic analysis of the SG glomeruli reveal that (1) the primary trigeminal axonal endings differ morphologically from those in other sites in the main sensory and spinal trigeminal nuclei and (2) that they are linked synaptically to three different kinds of dendritic processes and an axonal process. Primary axonal endings form axodendritic synapses on two kinds of dendritic spines and on dendritic shafts. These dendritic processes are linked by two kinds of dendrodendritic synapses. Type 2 dendritic spines contain large synaptic vesicles in their spine heads and form dendrodendritic synapses on type 1 spines. In addition type 2 spines also form dendroaxonic synapses on the primary trigeminal nerve endings. Dendritic shafts, containing small synaptic vesicles form dendrodendritic synapses on type 1 spines and amongst themselves. Small axonal (P) endings containing small synaptic vesicles form axoaxonic synapses on the type 1 spines and dendritic shafts.

The presence of dendroaxonic and axoaxonic synapses in the SG glomeruli suggests that there is integration of input taking place on the axolemma of primary trigeminal axonal endings. These relate to incoming action potentials, excitatory synaptic potentials and inhibitory synaptic potentials, all of which affect the quantity and time course of transmitter release at the axodendritic synapses of primary trigeminal axons.

Current circuit diagrams of nucleus caudalis presume that each of its three layers contains a single neuronal cell type. Our EM and Golgi studies suggest that the synaptic organization is far more complex, involving many different neuronal cell types. For example, the presence of two different kinds of synaptic vesicle-containing dendrites in the SG glomeruli indicates that there must be at least two different kinds of neurons which send their dendrites into the SG layer.

The results of a series of Golgi studies in adult cats have revealed that three kinds of neurons are found in the SG layer. These neurons are distinguished from each other by their dendritic branching pattern, spine distribution, axonal branching pattern and the distribution of their axons and dendrites in the three layers of nucleus caudalis. They include (1) the islet cell, a neuron whose dendrites and axons are confined within the SG layer; (2) the stalked cell, a neuron whose dendrites and axon is distributed in the SG and marginal layers and (3) the spiny cell, a neuron which sends dendrites and axons into all three layers of nucleus caudalis. The axons of these neurons do not project out of nucleus caudalis and these neurons are identified as interneurons i.e. Golgi type II neurons which are interposed in afferent axon-projection neuron circuits through nucleus caudalis.

In addition to these three intrinsic neurons, neurons in the marginal and magnocellular layers also send their dendrites into the SG layer. Some of these marginal and magnocellular neurons are second-order projection neurons and send their axons out of nucleus caudalis.

In Golgi studies of the marginal layer, four distinct neuronal cell types have been identified. These include two projection neurons and two interneurons. The projection neurons are located in the upper half of the marginal layer and are distinguished by their dendritic arbors. One type, the Waldeyer cell, has an extensive dendritic arbor which descends through the SG layer into the magnocellular layer while the other projection neuron, the limitrophe cell, sends its dendrites only to the medial border of the SG layer. The axons of the Waldeyer and limitrophe cell project out of nucleus caudalis via the spinal trigeminal tract. The two interneurons of the marginal layer are found in the lower half of the marginal layer and are distinguished by their dendritic branching pattern, spine distribution and axonal branching pattern.

Our current efforts are aimed at correlating more precisely the neuronal cell types identified in the Golgi studies with the neural elements of the SG glomeruli identified in the EM studies. In addition current Golgi studies seek to identify the neuronal cell types in the magnocellular layer and to provide information about their dendritic and axonal arbors.

Correlative anatomical and physiological studies have been concerned with the morphology of receptors associated with stiff hairs on the monkey's face that respond to weak mechanical stimuli. Slowly-adapting (SA) responses recorded from dissected strands of the infraorbital nerve were histologically-verified to be associated with sinus and non-sinus hairs found above the lip. Two types of SA responses could be distinguished on the basis of

spontaneous activity, regular or irregular discharge patterns, and the presence or absence of maintained activity for more than 90 sec to mechanical displacement of the hair or adjacent skin. Non-sinus hairs on the face that exhibit slowly-adapting responses are unique. The present studies of non-sinus hairs were done in collaboration with Dr. Bryce Munger of the Hershey Medical Center and were found to have a Ruffini-like ending tucked under the sebaceous gland. In addition, some of these hairs were innervated in the basal layer of the epithelium of both the uppermost part of the follicle, and the surrounding rete pegs. At these locations, Merkel-cell-neurite complexes were found.

Most hair receptors with slowly-adapting responses are associated with facial sinus hairs. In the monkey, these hairs exhibit multiple receptor types as do the sinus hairs of the rat and rabbit. Merkel-cell-neurite complexes and lanceolate endings are present. In addition, a structure that exhibits some of the anatomical properties of the Ruffini ending found in the non-sinus hair is being studied.

Psychophysical and Clinical Studies

These studies are in their initial stages and involve two areas of research: (1) assessment and measurement of experimental and clinical acute pain, and (2) psychophysiological evaluation of intravenous sedation agents for oral surgery procedures in ambulatory dental patients. The studies of pain measurement and assessment involve the development of methods of scaling the sensory and affective components of the pain experience. Experimental pain stimuli (electrocutaneous, electric tooth pulp, and conductive heat) are scaled by the psychophysical methods of magnitude estimation, category scaling, cross modality matching, and signal detection. Acute dental pain is scaled utilizing pain questionnaires, category scales, and by means of direct sensory matches to experimental pain stimuli. Questions of interest are: (1) Can the sensory and affective components of experimental and acute dental pain be separated and independently scaled? (2) Are experimental pain models adequate analogs of acute dental pain? (3) What are the relative ranges of experimental and clinical pain scales?

Other psychophysical studies of pain in humans were carried out to evaluate first and second pain. Abrupt, short-lasting noxious stimuli are common in every day experience. Often such stimuli produce an initial sharp pain called first pain, followed by a burning or throbbing pain called second pain. Experiments were carried out on human subjects to determine how first and second pain are influenced by parameters of peripheral stimulation. For these experiments, brief painful stimuli delivered to the hands or feet were constant waveform heat pulses that raised skin temperatures to noxious levels (45-49^{0}C) for 0.7 sec. Reaction time measurements confirmed that first and second pains could be accounted for by impulse conduction over Aδ (finely myelinated) and C (unmyelinated) fibers, respectively. This was further substantiated by selectively blocking first pain by compression of nerves for 30-40 min.

Sensations of second pain increased with each successive thermal stimulus if these stimuli were delivered more often than 0.3 per sec. This progressive increase also could be elicited after blockade of first pain. In contrast, first pain decreased with each successive thermal pulse when such stimuli were delivered at rates of 0.5 per sec and 0.2 per sec. All of these results point to distinct functional differences between first and second pain. Second pain is more labile than first pain in that it summates at low stimulus frequencies (>0.3 per sec). On the other hand, first pain decreases in intensity with each successive stimulus but only if initiated by noxious heat at the same skin location. This phenomenon is most likely related to the susceptibility of Aδ heat nociceptors to suppression by repeated stimulation.

The studies on the efficacy of intravenous sedative agents will develop drug combinations which will provide amnesia, maximum physiological safety, and rapid postoperative recovery for ambulatory dental patients. Measurement of the effect of these pharmacological agents on sensory function, psychomotor performance, cognitive function and memory will be assessed utilizing various psychological tests. Preliminary studies indicate that the combination of diazepam (tranquilizer), sublimaze (ultra-short acting narcotic) and methohexital (ultra short-acting barbiturate) produces amnesia without loss of consciousness. In addition, there appears to be considerable impairment of sensorimotor and cognitive functions immediately after surgery.

Future Plans

Our behavioral and physiological studies will continue to focus on central nervous system coding mechanisms of pain sensation and reaction. Experiments in awake monkeys will attempt to correlate neural events in the trigeminal brainstem nuclear complex with escape behavior to noxious thermal stimuli. The effect of the manipulation of motivational factors and/or analgesic agents (morphine, central brain stimulation) on behavior and central neural events will be studied. Anatomical studies will continue to unravel the neuronal circuity of trigeminal nucleus caudalis using various new light and electron-microscopic techniques. These studies also will be correlated with electrophysiological experiments so that functional correlation of individual neuronal cell types in trigeminal nucleus caudalis can be made. Clinical and experimental pain studies will continue to develop and validate new methods of pain measurement and assessment. Validated measures will be used to assess the mechanism of action of currently-accepted drugs used in pain control as well as evaluating the efficacy of various new non-pharmacological pain control agents.

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Summary Report of the Clinical Investigations and
Research Services Branch
National Institute of Dental Research

During the two years since its inception, the Clinical Investigations and Research Services Branch has been primarily concerned with developing an integrated clinical research enterprise which utilizes existing clinical resources both directly and via collaborative efforts with other NIDR branches and laboratories. In addition to this function, the Branch has also retained the responsibility for maintaining clinical dental services for the NIH Clinical Center.

Since this latter responsibility is largely independent of future plans to develop a program emphasizing clinical diagnosis, administrative responsibility for the Clinical Dental Services Section is to be transferred directly to the Office of the Clinical Director in the near future.

In general, the Branch has succeeded in its primary goal of establishing firm collaborative research commitments with LMI, NAB and LOM. Nearly all of the new projects initiated within CIR have been productive with most already yielding results which are being compiled for publication.

Future plans for the Branch are based on a more complete disassociaton of research efforts from clinical dental service responsibilities per sé wherein a new section comprised of an interdisciplinary research team will direct primary effort toward isolation of factors limiting diagnostic performance. This will be done by modeling diagnostic systems in a task-specific way and testing resulting predictions in clinically meaningful situations.

Research pertaining to the functional relationships existing between various oral and pharyngeal structures during development will continue to be emphasized in a way which is consistent with the many recent accomplishments noted in the report of the Oral and Pharyngeal Development Section. To this end, newly developed technical resources under investigation for potential diagnostic applicability are also being made available for research purposes within the program.

Report of the Clinical Dental Services Section
Clinical Investigations and Research Services Branch
National Institute of Dental Research
Summary Statement
1975

The Clinical Dental Services Section continues in the dual mission of providing dental services and dental research within the overall NIDR effort. Due to limitations in professional staff, the Dental Clinic provides dental consultation and only the more essential service therapies for Clinical Center patients. A variety of dental research projects are originated by personnel within this section. Collaborative dental research programs are conducted with NIDR scientists as well as scientists outside NIDR. A definite emphasis has been placed on dental research since reorganization in August, 1973.

Within the past year three studies have been completed and are being prepared for publication. One deals with the radiographic visibility of induced skull fractures. This project was a collaborative effort with Dr. John Doppman of the Clinical Center Diagnostic Radiology Department. The second was an electron microprobe and x-ray diffraction study of the gamma^2 (mercury-tin) phase present on dental amalgam surfaces. This dental restoration corrosion study was done in collaboration with Mr. Richard Waterstrat, ADA Research Associate, National Bureau of Standards, and Drs. Eanes and Greenfield of the Laboratory of Biological Structure. The third completed project involved the relationship of herpes simplex virus and interferon in human gingival cell cultures. This collaborative study was performed with Dr. Samuel Baron, Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases.

Dental research projects originated by this section's personnel have been under study for the past 21 months and are in varying stages of completion. These are as follow:

Rhesus Monkey Intraosseous Implant Study (Pilot Study Completed - general study in progress)

The effect of functional occlusal loading on supporting tissues is being assessed in a controlled fashion through serial quantitative radiographic analysis of apparent calcification of subjacent bone, and terminal histological examination of both splinted and free-standing acrylic implants. Tetracycline antibiotic is being evaluated as microbacteriological control agent.

Lavage Volumes in Third Molar Surgery

Clinical evaluations are being performed on the effects of various lavage modalities on post-surgical healing of third molar extraction sites.

Transient Bacteremias Related to Oral Surgical Procedures

Four different projects are combined in this multifaceted study. They involve respectively:

a. Effects of topical pretreatment of surgical areas with various antiseptics on the induction of bacteremias.

b. Application of the nitroblue tetrazolium dye test in evaluating surgically induced bacteremias.

c. Comparative evaluation of blood culture media for the recovery of anerobic organisms.

d. Evaluation of endo-toxemia in transient bacteremias.

These combined projects are being done in collaboration with Drs. Brenner and Elin of the Clinical Pathology Branch of the Clinical Center and Dr. Chusid of the Laboratory of Clinical Investigations, NIAID.

Evaluation of Immunological Parameters of Human Subjects with Periodontal Disease

Pre-and post treatment comparisons of lymphocyte transformation reactivity to plaque antigens, soft tissue T and B lymphocytes and specific antibody response mechanisms are being made.

This project is in collaboration with Drs. Oppenheim and Chused of the Laboratory of Microbiology and Immunology, NIDR and Drs. Baker and Chan of Litton Bionetics, Bethesda, Maryland.

At least five extra-section groups from NIDR are presently collaborating with our section personnel on clinical research projects. These groups and their activities are as follows:

Clinical Immunology (salivary gland studies of Sjogren's patients, HLA antigens correlated with periodontal disease incedence and immunologic parameters of periodontal disease); Clinical Virology (oral ulcerative lesions); Laboratory of Microbiology (dental plaque diseases-screening methods and control therapy); Laboratory of Neurobiology and Anesthesia (psychophysical evaluations of dental patients and pain control); Clinical Investigations Section (methodology related to x-ray enhancement).

As the NIDR Intramural research program continues to develop, the Dental Clinic can continue to offer the unique and essential opportunity to provide a link between basic research laboratory activities, clinical research laboratory activities and the clinical human patient disease problem.

Summary Report of the Clinical Investigations Section
Clinical Investigations and Research Services Branch
National Institute of Dental Research

The Clinical Investigations Section as originally comprised was a multidisciplinary enterprise which combined the professional talents of basic scientists with research oriented clinicians for the purpose of initiating and facilitating clinical research. The main thrust of the group was to develop and implement diagnostic standards applicable to clinical investigations of all types. Practical limitations have limited research efforts to two major areas, one involving microbiological analysis of infectious dental diseases and the other centered around the determination of factors limiting diagnostic performance from a systems point of view.

With the establishment of a new unified section of Microbiology in the Laboratory of Microbiology and Immunology, the microbiological activity being done in the Clinical Investigations Section was recently transferred to LMI. This permitted a more unified approach to clinical studies based on microbiological observations by assuring greater availability of existing expertise and resources in this area. It also provided a sound basis for developing a more unified program in systematic research per sé since the section (soon to be designated Diagnostic Methodology) is no longer functionally involved in two largely independent areas of activity.

Clinical investigations involving microbiological assay of Streptococcus mutans from clinic patients and normal controls has yielded preliminary data which does not suggest a close correlation between the prevalence of S. mutans as scored and the status of caries activity as recorded in the conventional examination of patients.

Phase contrast examination of samples of plaque from patients with and without periodontal lesions indicates that various types of motile bacteria (spirochetes, motile rods, and other forms) are prevalent in areas where lesions are present. Very long motile rods appear to be present in deep pockets, especially those that appear to be rapidly advancing. Multiple observations suggest that the presence of such motile forms does not seem to be significantly influenced by continued scaling and curettage of pockets and good supragingival plaque control.

Preliminary studies involving the administration of tetracycline systematically for two weeks (250 mg qid) indicate that the prevalence of motile bacteria and inflammatory cells can be reduced to low levels in periodontal pockets. This appears to be accompanied by a significant decrease in gingival inflammation.

Clinically applied saturated solutions of sodium chloride or sodium bicarbonate have been shown to cause rapid cessation of motility in spirochetes and in almost all other motile rods. Conscientious use of such solutions by patients in a rigorous home care self-application scheme has resulted in minimal supragingival plaque with no evidence of spirochetes or motile rods.

Preliminary observations involving periodontal patients who have received both tetracycline therapy and the soda-salt regimen, suggest that they improve clinically to an extent which may be greater than when either therapy is used singly. Hence, the respective therapeutic value of antibiotics and saturated salt solutions warrants further study.

In addition to this work, a comprehensive review paper on the value of fluoride therapy in the treatment of dento-bacterial plaque disease was prepared by Dr. Paul Keyes in collaboration with Dr. Harold Englander and has been published in the *Journal of Preventive Dentistry*.

Research directed toward improved identification of factors limiting diagnostic performance likewise has progressed through systematic analysis of the role of spatially invarient transformations of images known to contain information of diagnostic interest. Recent findings confirm that diagnosis of incipient carious lesions from dental radiographs is not limited by the information capacity of the radiographic system. Moreover spatial frequences essential to diagnosis of known lesions have been shown to lie below the limit imposed by conventional film-screen combinations. Hence, it is possible to reduce the exposure required for bitewing type radiographs by a factor of twenty or more with little degradation in measured diagnostic performance.

A prototype system capable of such performance has been tested extensively using in vitro techniques and recent efforts have shown that the system can be applied clinically as well.

It is based on a modified intraoral source which can be selectively collimated for various specific clinical applications. Hence, one basic source can be used for applications which traditionally require multiple exposures from one or more X-ray machines. By placing the image transducer outside the mouth, it is possible to optimize performance in a task-specific way to the extent that for many applications images can be processed and viewed seconds after exposure under ordinary room lighting conditions.

These and other efforts can be predicted with the aid of a computer simulation program currently under development in cooperation with the Bureau of Radiological Health. Similarily software capable of three-

dimensional analysis of a two-dimensional multiaxial tomographic array is being applied to diagnostic tasks of dental interest. This work is being done in collaboration with the U.S. Air Force School of Aerospace Medicine.

Other work has involved abstraction of growth data from cephalometric radiographs with the aid of a new geometry of form recently developed by Mr. Harry Blum of the Division of Computer Research and Technology. Preliminary findings suggest that description of anatomical relationships in this way may be more efficient while at the same time providing important clues to developmental processes responsible for the observed shape of the structure under consideration.

Three papers have been submitted for publication in these areas within the last year and two others are in various stages of preparation. Even greater productivity can be expected in the long run by virtue of the fact that a full-time computer scientist is currently being recruited to facilitate more rigorous analysis of pertinent data.

To this end, most recent efforts have been directed toward establishing a laboratory computer facility to buffer and analyze diagnostic information obtained from a variety of clinical sources.

Report of the Oral and Pharyngeal Development Section
Clinical Investigations and Research Services Branch
National Institute of Dental Research
Summary Statement

The activities of this Section continue to be concerned with the development of structure and of function in the oral and pharyngeal area.

This is the sixth year of gross anatomical studies of the mouth, pharynx and cranium of the human fetus at term. An Atlas of Anatomic Sections and Tomograms of the Infant Cranium is under review by a private publisher.

Illustration and text drafting of a general anatomy of the face, pharynx and larynx of the newborn continue. The final unit of illustration, of the larynx and lower pharynx which will complete this volume, is now in progress.

The text of the atlas, Development of the Rat Skull (by Melvyn M. Baer, James F. Bosma and James A. Ackerman) is undergoing final editing. Grant application for sponsorship of this publication will be submitted to the National Library of Medicine Extramural Program prior to October 1, 1975.

The psychophysical studies of oral reflexes of the infant have continued. The role of sweet (glucose) solute in elicitation of the specific transverse tongue response has now been worked out. Comparable elicitation effects have now been found for saline (sodium chloride) solutions.

We continue our efforts of conference assembling of investigators concerned with the development of oral sensation and perception. J. Weiffenbach arranged and conducted a Symposium on Development of Sweet Preference in June, 1974. Accumulation of this materiel is essentially completed; the volume should be in press, in the Government Printing Office, in June. On invitation, Dr. Weiffenbach arranged and conducted a smaller informal conference on Taste in the Newborn at the meeting of the Eastern Psychological Association in April, 1975; publication of this, in summary form, will be in a journal. The next symposium on this theme is now in plan, for summer, 1976.

The Fourth Symposium on Oral Sensation and Perception: Development in Fetus and Infant was off the press in June, 1974, from the Government Printing Office. A smaller symposium on this topic was arranged and conducted by J. Bosma at the American Association of Dental Research in April, 1975. A Fifth Symposium is in plan.

The NIDR, in cooperation with the National Institute of Child Health and Human Development, and the Fogarty International Center, sponsored a Symposium on Development of Upper Respiratory Form and Function, in April, 1974; this has been accepted for commercial publication. The work of our group on development of sensorimotor functions was included in a University of Michigan Symposium on Oral Development, in April, 1974; this chapter is published in the Moyer's Symposium on Craniofacial Development, March, 1975.

We continue consultations with Clinical Center patients of other Institutes, particularly apropos of disabilities of the pharyngeal area. J. Bosma also continues working in collaboration with the Departments of Radiology and Neurology of the Johns Hopkins Medical Center in a study of pharyngeal disabilities of the human child and adult.

PART V

NATIONAL INSTITUTE OF DENTAL RESEARCH

ANNUAL REPORT

COLLABORATIVE RESEARCH PROJECTS

July 1, 1974 - June 30, 1975

Compiled By

Dental Research Data Officer

National Institute of Dental Research

National Institutes of Health

Bethesda, Maryland

Preface

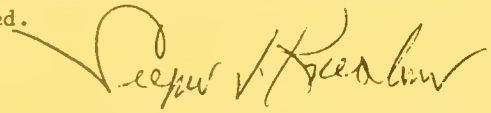
Progress in scientific research is often so subtle that it escapes notice--and the achievements of those individuals who support that research are even less obvious. Only when dramatic discoveries are announced do the contributors to that effort gain some bit of recognition. Still, on a day-to-day basis many dedicated people are working diligently toward that eventual break-through. The annual report at NIH provides each participant in the organizational research effort with an opportunity to reflect on, evaluate, and document their contribution to science on an annual basis. This NIDR Annual Report is a record of our Institutes' activities and progress during fiscal year 1975.

For convenience in compilation and distribution, the Report is prepared in five volumes; Part I, Office of the Director and Research Projects and Indexes; Part II, National Caries Program; Part III, Extramural Programs; Part IV, Intramural Research; and Part V, Collaborative Research Projects. This is the fourth year that we have combined the individual project report with the SSIE Notice of Research Project form (PHS 166) and find it most effective for our needs. These are printed on blue paper as a separate section of Volume I.

The numbering system has been changed slightly this year to conform with the NIH-wide practice for numbering grants and contracts. All intramural research projects will bear the same number during their life time and will have a "Z01" prefix. The two digits immediately following the five-digit number indicate the number of years that the project, or some identifiable portion of that project, has been active.

It should be pointed out that while the NIDR Annual Report is not a restricted document, it was prepared for administrative use at NIH and not for public distribution. No attempt has been made to evaluate the quality of research--this has been done by study sections, advisory groups or laboratory and branch chiefs--and the comments of the various contributors to this document are their own.

Recipients of this Report are encouraged to familiarize themselves with the Contents and Indexes and constructive criticism aimed at its overall improvement will be welcomed.



Seymour J. Kreshover, D.D.S., M.D.
Director
NIDR

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COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 AI52530-00
ORGANIZATION	BETH ISREAL HOSPITAL
ADDRESS	BOSTON MA
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	FREEDBERG, IRWIN M
NIDR PROJECT OFFICER	PAYNE, FRED J
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

THERAPY OF CUTANEOUS HERPES SIMPLEX IN NORMAL & COMPRISED HOSTS

OBJECTIVES AND WORK SCOPE

Independently and not as an agent of the Government, the Contractor will conduct studies to better define the natural history of facial mucocutaneous herpesvirus hominis infections and to determine the safety and estimate the efficacy of monophosphate adenine arabinoside and disodium phosphonoacetate when used topically in the treatment of confirmed facial mucocutaneous herpesvirus hominis infections. The work will be done in two phases.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 AI52531-00
ORGANIZATION	UNIVERSITY OF MIAMI
ADDRESS	MIAMI FL
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	BLANK, HARVEY
NIDR PROJECT OFFICER	PAYNE, FRED J
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

DRUG EFFICACY STUDY - MUCOCUTANEOUS HERPES INFECTIONS

OBJECTIVES AND WORK SCOPE

The purpose of this study is to determine the efficacy of ARA-A and Phospholoacetic acid in the treatment of facial mucocutaneous Herpes simplex virus infections in a double blind controlled study. The drugs will be administered topically.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 AI52532-00
ORGANIZATION	UNIVERSITY OF UTAH
ADDRESS	SALT LAKE CITY UT
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	OVERALL, JAMES C
NIDR PROJECT OFFICER	PAYNE, FRED J
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

STUDY OF RECURRENT MUCOCUTANEOUS HERPERSVIRUS HOMINIS INFECTION

OBJECTIVES AND WORK SCOPE

Independently and not as an agent of the Government, the Contractor will conduct studies to better define the natural history of facial mucocutaneous herpesvirus hominis infections and to determine the safety and estimate the efficacy of monophosphate adenine arabinoside and disodium phosphonoacetate when used topically in the treatment of confirmed facial mucocutaneous herpesvirus hominis infections. The work will be done in two phases.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE02238-06
ORGANIZATION	FRANKLIN INSTITUTE
ADDRESS	PHILADELPHIA PA
INITIAL START DATE	06-26-70
EXPIRATION DATE	07-31-74
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	THELEN, EDWARD
NIDR PROJECT OFFICER	VALEGA, THOMAS M
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

STUDY OF ADHESIVE MECHANISM DIFFERENT SPECIES SEA MUSSEL

OBJECTIVES AND WORK SCOPE

Independently and not as an agent of the Government, the Contractor shall exert its best efforts to determine the chemical and physical properties of the cementum of marine organisms including the mussel and barnacle in both the hardened and unhardened state, for use in synthesizing similar products which will be useful in dentistry. The Contractor shall also maintain mussel and barnacle colonies and other organisms as required by the study. The Contractor shall furnish small quantities of cement(s) to the Government for testing at regular intervals when they believe they have a cementitious product ready for dental testing.

SALIENT RESULTS TO DATE

Work so far has shown that byssus is a crosslinked protein. Solutions derived from arca byssus are characterized by a distinct yellow color and by marked fluorescence. These features are also observed in elastin. It is possible, therefore, that the material contains some of the crosslinks found in elastin. These include the desmosines and the isodesomines which have characterisitc U.V. absorption and can be isolated by ion exchange. It appears byssus in not homogeneous. Loose filaments lying between fivers may represent the water soluble fraction whose function could be to cement the fibers into sheets.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12062-06
ORGANIZATION	UNIVERSITY OF PUERTO RICO
ADDRESS	SAN JUAN
INITIAL START DATE	12-30-70
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	HARRIS, NORMAN O
NIDR PROJECT OFFICER	FREW, RALPH A
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

EVALUATION OF AN ADHESIVE SEALANT MATERIAL

OBJECTIVES AND WORK SCOPE

This project is designed to evaluate the anticaries potential of an adhesive sealant in a dental public health program. The sealant is placed in children's teeth by various types of dental auxiliary personnel under a variety of field conditions in the Virgin Islands. Baseline and follow up examinations will define the efficacy and persistance of the agent under the operant conditions. the project is entering its third year. The first year involved baseline examinations and treatment of the study population. The activity for subsequent years is primarily involved with the reexamination of the study population.

SALIENT RESULTS TO DATE

The treatment phase of the program began in the spring of 1971 and was completed during the spring of 1972, and the first followup examinations were conducted. Data from these examinations reflecting 6 months to one year's experience have been processed. Retention rates of from 30% to 80% depending on individual applying the material, type of site sealed and location of the site were found. The second followup examination reflecting 18 to 24 months experience was completed during the previous year (1973). Retention rates decreased from 10% to 30% by site from the first year's retention rates. Caries reductions approximated the retention rates for most sites.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12093-05
ORGANIZATION	HEALTH RESEARCH, INC
ADDRESS	ALBANY NY
INITIAL START DATE	05-17-71
EXPIRATION DATE	04-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	CONS, NAHAM C
NIDR PROJECT OFFICER	FREW, RALPH A
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

ADHESIVE SEALANT FIELD TRIAL

OBJECTIVES AND WORK SCOPE

The workscope remains the same, except that portion dealing with tests on 100 children using fiberoptics has been deleted, i.e., item 6 of the Description of Work.

SALIENT RESULTS TO DATE

After one year's experience with the sealant, the data was analyzed. One of the objectives of the study was to measure the time required to place the sealant in a molar. As a result, the average time needed to seal a molar was eight (8) minutes and fifteen (15) minutes for two molars; overall retention was good. Also, IBM scanning forms were received by NIDR. After corrections were made to the data for the period 1973-74, they were sent to NIDR. Upon completion of examining the data by NIDR, a report will be issued to Health Research, Inc.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12330-04
ORGANIZATION	SOUTHERN ILLINOIS UNIVERSITY
ADDRESS	EDWARDSVILLE IL
INITIAL START DATE	06-30-71
EXPIRATION DATE	03-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BAHN, ARTHUR N
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

IMMUNIZATION WITH ENZYMES FROM CARIOGENIC STREPTOCCI

OBJECTIVES AND WORK SCOPE

Contractor will exert best efforts to isolate and purify dextransucrases, levansucrases, and glycosidic hydrolases, from cariogenic streptococci, which will be investigated for their effectiveness as immunizing agents to reduce experimental dental caries.

SALIENT RESULTS TO DATE

Two rat experiments, completion of one monkey experiment and initiation of a csecond monkey experiment were undertaken during the second contract year. A highly purified levansucrase injected into rats showed reduction in caries only if injected at weekly intervals. A glycosidic hydrolase preparation injected into rats elicited high-titered antibody neuraminidase. Reductions in radiographically-detectable and clinical caries were obtained in monkeys. No apparent pathological changes were observed in the monkeys. The second monkey experiment has been designed to test all three enzyme groups as anti-caries immunogens. Highly painstaking and detailed investigations have been involved in the current year of the contract but progress has been excellent.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE12331-04
ORGANIZATION	UNIVERSITY OF MINNESOTA
ADDRESS	MINNEAPOLIS MN
INITIAL START DATE	06-29-71
EXPIRATION DATE	12-28-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	SCHACHTELE, CHARLES
NIDR PROJECT OFFICER	ROUSSOS, GERASSIMOS
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

ANTIMICROBIAL AGENTS AFFECTING CARIOGENIC MICROORGANISMS

OBJECTIVES AND WORK SCOPE

Contractor will exert best efforts to investigate unique features of the membrane-associated phosphotransferase sugar uptake system of oral cariogenic bacteria and to analyze for antimicrobials which could inhibit this system.

SALIENT RESULTS TO DATE

Membranes prepared from decryptified S. mutans cells have been found to contain a constitutive glucose transport system that is absolutely dependent on PEP. The membrane preparations do not possess dextral or levan sucrose activity. The membrane glucose transport system of four strains of S. mutans and eight other oral microorganisms was found to be similar and their activity was compared. In each case, PEP is used to phosphorylate the C-6 position of glucose in a reaction that is insensitive to fairly high concentration of fluoride. However, PEP production by enolase, an intracellular enzyme, is blocked by this enzyme. Several sugars, including glucose-6-P and glucose-1-P, have been found markedly to inhibit the phosphotransferase system. Two new procedures have been worked out that will allow the research to proceed more rapidly. The first of these is a preparation of active membranes by toluene treatment rather than freeze-drying; the second is an assay for enzymatically phosphorylated sugars by adsorption to DEAE-cellulose discs which are washed, dried, and radio assayed. Work on the fructose transport system and on the inhibition of sugar transport is continuing.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12332-03
ORGANIZATION	MEDICAL COLLEGE OF GEORGIA
ADDRESS	AUGUSTA GA
INITIAL START DATE	06-29-71
EXPIRATION DATE	06-28-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BURNETT, GEORGE
NIDR PROJECT OFFICER	SHERN, ROALD J
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

TESTS OF ANTICARIES EFFICACY OF CERTAIN AGENTS

OBJECTIVES AND WORK SCOPE

Contractor will exert its best efforts to search for and obtain potential anticaries agents from pharmaceutical companies and conduct in vitro and in vivo tests of the anticaries efficacy of these agents.

SALIENT RESULTS TO DATE

In the past year, the additional studies were done so that about 60 compounds have been screened in the past two years. They have identified 11 compounds which warrant further investigation. Of these, at least two will be tested in short term clinical trials.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12375-07
ORGANIZATION	FORSYTH DENTAL CENTER
ADDRESS	BOSTON MA
INITIAL START DATE	06-28-71
EXPIRATION DATE	03-01-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DE PAOLA, PAUL F
NIDR PROJECT OFFICER	HEIFETZ, STANLEY B
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

TOPICAL USE OF ACIDIFIED NH4F VS. ACIDIFIED NAF

OBJECTIVES AND WORK SCOPE

The Contractor will compare the relative caries inhibitory effect of supervised, daily, one-minute mouth rinses in school with 5 ml of NH4F, pH4.4 containing 5 mg of F ion, and determine fluoride uptake in subjects receiving the foregoing treatments and to relate fluoride uptake to caries experience on a group basis.

SALIENT RESULTS TO DATE

Completion of the third semi-annual applications. Completion of 12-month follow-up clinical and radiographic examinations. Clinical and biopsy data are currently being processed. No caries protection has, as yet, become apparent in either of the test groups. However, because of the slow rate of development and progression of dental caries, field clinical trials are usually conducted for a minimum of two years. Progress has been satisfactory and proceeds according to protocol.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE12377-07
ORGANIZATION	UNIVERSITY OF TEXAS AT HOUSTON
ADDRESS	HOUSTON TX
INITIAL START DATE	06-30-71
EXPIRATION DATE	12-28-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DREIZEN, SAMUEL
NIDR PROJECT OFFICER	STILES, HORACE M
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

EFFECT OF XEROSTOMIA ON HUMAN ORAL MICROFLORA

OBJECTIVES AND WORK SCOPE

Prime objectives are: 1. Clarify the saliva-microbial-dental caries relationship by: a. Delineating the general characteristics of the oral microbial population changes in patients with radiation induced xerostomia b. Identifying the specific changes in the occurence and numbers of those microorganisms which have been implicated in the caries process. c. Elucidating the effect of caries preventive agents and procedures onf the oral microflora in patients with radiation induced xerostomia. 2. Establish a human model system for the rapid screening of anticaries agents in the presence of unusally potent caries challenge. Determine the fluoride level in plaque in individuals studied at time of postradition. Determine titrations of total acidity produced by the plaque suspensions. Analyze the lactate produced by the suspensions and specific microbial isolates. Place remaining entering study subjects on sucrose free diet. During the first 6-8 weeks of regimen, plaque specimens shall be monitored at 2-week intervals.

SALIENT RESULTS TO DATE

A total of thirty patients are currently being followed on a longitudinal basis to ascertain the effects of radiation induced xerostomia on the oral microflora. Half of these patients were placed on a daily topical application of 1% sodium fluoride gel and the other half placed on a non-fluoride gel of otherwise identical composition. Eight of the "non-fluoride" gel patients have been transferred to the fluoride gel at either six, nine, or twelve months postradiation because of impending rampant caries. The mean DMFS increase in the non-fluoride group has been 2.51/month as compared to 0.18/month for the fluoride group. The same value for the non-fluoride group was 0.30/month. Although there is a difference in caries increment between the fluoride and the non-fluoride groups, the oral microbial picture is essentially the same. An additional nine patients have been added to the study during the third contract year. The effect of a combined dietary sugar restriction and fluoride gel use is presently being assessed in these patients. Results from this phase of the study are not conclusive since they represent a limited period of observation. An additional year is needed to assess the long term effect of this regimen.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12379-06
ORGANIZATION	FORSYTH DENTAL CENTER
ADDRESS	BOSTON MA
INITIAL START DATE	06-28-71
EXPIRATION DATE	12-31-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DE PAOLA, PAUL F
NIDR PROJECT OFFICER	DRISCOLL, WILLIAM S
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

NH4F MOUTH RINSE VERSUS HIGH-POTENCY FLUORIDE RINSE

OBJECTIVES AND WORK SCOPE

To quantify plaque and gingival conditions, the clinical examinations will also include the Green and Vermillion and the Russell Periodontal Index. This information will be correlated with the other measurements obtained in the study.

SALIENT RESULTS TO DATE

Mouth rinses continued during school days. Twelve-month follow-up clinical, radiographic, and biopsy procedures were completed. DMFS and biopsy data are currently being statistically evaluated. The data shows a moderate reduction of caries increments in the test groups. However, because of the slow rate of development and progression of dental caries, field clinical trials are usually conducted for a minimum of two years. Progress is satisfactory and proceeding as per protocol.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE12380-04
ORGANIZATION	UNIVERSITY OF ALABAMA
ADDRESS	BIRMINGHAM AL
INITIAL START DATE	06-28-71
EXPIRATION DATE	06-27-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	FINN, SIDNEY
NIDR PROJECT OFFICER	FREW, RALPH A
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

STUDY OF TRIMETAPHOSPHATE ON PLAQUE

OBJECTIVES AND WORK SCOPE

Objective of study is to establish and measure anticaries activity of Sodium Trimetaphosphate (STMP) when topically applied to the dentition of children in a chewing gum vehicle. The gum will be distributed to approximately 600 children participants on a systamatic basis with oral examinations to be conducted prior to the study and at 6 month intervals thereafter. Both clinical and radiographic results will be observed and recorded by the Contractor, and transmitted to NIDR for processing and analysis of the data in-house. All children will receive a dental prophylaxis prior to each examination.

SALIENT RESULTS TO DATE

Supplying and dispensing of the gum during the school and vacation periods, supervising the chewing perids during school, and providing the required clinical and radiographic examinations for each child has been accomplished by the contractor during the previous year. Caries increments do not show significant differences between groups but treatment had been in effect for less than one year, and the increment found was not large. The microbiological examinations have failed to detect differences between study groups and this phase will be eliminated from the study unless the May, 1973, examinations show significant differences.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12381-03
ORGANIZATION	EASTMAN DENTAL CENTER
ADDRESS	ROCHESTER NY
INITIAL START DATE	06-29-71
EXPIRATION DATE	02-28-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	LOSEE, FRED L
NIDR PROJECT OFFICER	DRISCOLL, WILLIAM S
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

TRACE ELEMENTS CONTENT OF TEETH & CARIES SUSCEPTIBILITY

OBJECTIVES AND WORK SCOPE

Contractor will attempt to relate trace elements of teeth to their caries susceptibility by: 1. Selecting human teeth from geographic areas of high and low caries prevalence to determine the approximate concentrations in enamel and dentin of the major trace elements, together with calcium and phosphorus. 2. Analyses from residents of Colorado, Texas, New York, Ohio, Maine, and California will be reported. 3. Sufficient samples will be analyzed to provide information on intra-tissue distribution of elements so that a relationship can be established between trace element composition and resistance to caries. The following was added to the existing Scope of Work: Compare dietary factors with the trace element contents of teeth obtained from areas of high or low caries prevalence. Food, water, and other environmental sources of trace elements will be collected from areas where a dietary reconnaissance visit is made. Analysis of the trace element contents of these samples will be performed.

SALIENT RESULTS TO DATE

Established workable procedure for obtaining bicuspids was established. Data received with the tooth includes the DMFT status, age, sex, and water supply of the individual contributing the tooth. Critical examination of the enamel to be sampled was determined to be extremely important. It was found that with the inclusion of altered, stained (after pumice prophylaxis), or carious enamel would increase the concentration of several elements depending on the proportion of included sample. The F and Sr levels in enamel and dentin are both associated with the levels found in the water supplies. Fluoride and zinc concentrations are greatest in the surface enamel, whereas SR tends to be evenly distributed. Spark-source mass spectrographic technique appears to be a desireable means to look for 74 elements in a sample of only 1 mg. By using the Laser for excitation to present a plume of evaporated material to standard electric-arc emission spectrophotometry, it was shown that teeth from two different locations in California had differences in the enamels compositions of Al, Ag, Ba, Be, Cr, Cu, Ni, Pb, Sn, and Zn. A method for the determination of density has been worked out for enamel samples weighing 10 to 120 mg.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12383-06
ORGANIZATION	MIDWEST RESEARCH INSTITUTE
ADDRESS	KANSAS CITY MO
INITIAL START DATE	06-30-71
EXPIRATION DATE	09-29-74
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	BREED, L W
NIDR PROJECT OFFICER	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

STUDY OF ELASTOMERIC LINERS FOR DENTAL RESTORATIONS

OBJECTIVES AND WORK SCOPE

The Contractor shall screen various experimental polymers as dental restorative materials potentially useful as elastomeric liners or as composite filling bases capable of adhering to dentin and enamel. Optimal polymers as judged by in vitro adhesion tests shall be selected for in vivo testing in animals. Several polymer systems shall be tested in rats and in the teeth of dogs for the purpose of establishing toxic reactions, adhesive qualitites, marginal penetration, pulp reactions, and stability under oral conditions. In vivo results shall be correlated with in vitro tests.

SALIENT RESULTS TO DATE

The objective of the work has been to develop an acrylate-based formulation, which upon curing, has elastomeric properties, forms a coherent bond with tooth structure and dental restorative materials, and functions as a restorative liner. In vitro and in vivo screening of several formulations by the University of Missouri at Kansas City School of Dentistry revealed little or no marginal penetration in lined restorations and controls. Retention for both the lined restorations and the controls was good. Photographic evidence showed the presence of the liner between the cavity and the restoration and separation of the restoration from the cavity in unlined specimens. In the development of these formulations by Midwest Research Institute, in vitro tests for tensile strength of adhesion demonstrated poor adhesion for liner formulations modified with chelating polymers, and these formulations were abandoned. However, a number of formulations of the base elastomeric resins provided tensile strengths of adhesion of 1000 lb/in2 or more on phosphoric acidetched dentin. Compositional parameters in the restoration systems, which were important in determining the tensile strength of adhesion, included the crosslinking monomer, the initiator system, the commercial restorative used with the liner, and the application procedure.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE12386-05
ORGANIZATION	BATTELLE PACIFIC NORTHWEST LABORATORIES
ADDRESS	RICHLAND WA
INITIAL START DATE	06-30-71
EXPIRATION DATE	02-28-75
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	MARSHALL, ROBERT P
NIDR PROJECT OFFICER	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

DEVELOPMENT OF ARTIFICIAL DENTAL ANCHORS

OBJECTIVES AND WORK SCOPE

The contractor will study at least four materials as dental implants. This will include Titanium, void metal composite; Titanium, powder metallurgy product; Alumina porcelain; and Magnesium aluminate spinel. These materials will be charac terized by physical tests and implants designed to optimize desirable characteristics will be implanted in swine jaws and subjected to clinical and microscopic examinations to determine their clinical efficacy. A special scanning elec tron microscope examination of frozen-fractured specimens of the bone material interface will be performed.

SALIENT RESULTS TO DATE

Our study on the effect of constant, high sucrose diet on the streptococci composition of plaque shows that the percent of S. mutans increased over a 4 week period and that the percent of S. sanguis increased initially and then declined during a 4 week period. Further study of the clinical effects of the inclusion of sodium trimetaphosphate (TMP) in a high sucrose diet (200 g/day) showed that diets containing TMP produced apparent increases in mean values of lactobacilli, veillonella and neisseria per mg of plaque. High sucrose diets supplemented with TMP also produced an apparent decline in dextranase producing organisms per mg of plaque and increased the values of specific glucosetransferase and fructosyltransferase activities. Addition of TMP to typticase-soy agar plates appeared to decrease the colony size of S. sanguis 10558 but had no apparent effect on the colony sizes of S. mitis JC43, S. mutans BHT or MZ61.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE22003-06
ORGANIZATION	WORLD HEALTH ORGANIZATION
ADDRESS	1211 GENEVA 27
INITIAL START DATE	09-01-71
EXPIRATION DATE	01-31-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BARMES, DAVID E
NIDR PROJECT OFFICER	SENNING, RICKLEY S
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

ETIOLOGY OF DENTAL CARIES IN PAPUA-NEW GUINEA

OBJECTIVES AND WORK SCOPE

The Contractor will perform: A thorough and complete comparative evaluation in young human subjects of the test slab lesions as contrasted to natural lesions, utilizing all available procedures for measurement; A thorough and complete comparative evaluation in young human subjects of the microbial and biochemical compositions of test slab versus natural plaque; After the intraoral cariogenicity system has been sufficiently validated in the opinion of the Project Officer, a series of test variables may be imposed upon the model system to determine their relation to the promotion or inhibition of caries development.

SALIENT RESULTS TO DATE

All elements in saliva and enamel except lead and copper in enamel have been completed. The University of Sydney in association with WHO have developed suitable extraction and concentrating methods for lead and copper. It is anticipated these results will be available by 3/1/75. The analysis of fluoride and phosphorous in plaque is complete but definitive identification of all the important colony types present in plaque will be completed by 5/1/75.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22030-05
ORGANIZATION	UNIVERSITY OF ALABAMA
ADDRESS	BIRMINGHAM AL
INITIAL START DATE	11-15-71
EXPIRATION DATE	12-31-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	KOULOURIDES, T
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

EVALUATE INTRAORAL TEST OF HUMAN CARIOGENICITY

OBJECTIVES AND WORK SCOPE

The Contractor will perform: A thorough and complete comparative evaluation in young human subjects of the test slab lesions as contrasted to natural lesions, utilizing all available procedures for measurement; A thorough and complete comparative evaluation in young human subjects of the microbial and biochemical compositions of test slab versus natural plaque; After the intraoral cariogenicity system has been sufficiently validated in the opinion of the Project Officer, a series of test variables may be imposed upon the model system to determine their relation to the promotion or inhibition of caries development.

SALIENT RESULTS TO DATE

Seven sugars and sugar alcohols were compared to sucrose for cariogenicity when used as extraoral supplements to diets containing customary levels of sucrose. Regardless of the use of gauze overlays on the enamel surface, results corresponded well with those from rat feeding experiments at U.A.B. Fluoride at 10 PPM was more effective than at 1 PPM. Sodium glycerophosphate and TMP at 1% concentration added to 3% sucrose supplements abolished the cariogenicity of the sugar. If the enamel is softened by mild acid etch or by exposure to oral eivironment, the beneficial effect of fluoride was found increased. Fluoride biopsies showed selective deposition of fluoride in the 2-4 micron superficial layers of pre-softened enamel. Streptococcus sanguis appeared to be the primary colonizer for ICT and natural plaque formation. This same bacterial species appeared to be the primary colonizer at interproximal sites of both caries-free and caries-active children. Str. mutans was absent or in low numbers in ICT and natural plaques of caries-free subjects. Str. sanguis and salivarius predominate in the ICT plaques of both caries-free and caries-active subjects. Progress has been good but tends to be diffuse through examination of too many variables.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22400-02
ORGANIZATION	UNIVERSITY OF MIAMI
ADDRESS	CORAL GABLES FL
INITIAL START DATE	01-01-72
EXPIRATION DATE	12-31-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	ZINNER, DORAN D
NIDR PROJECT OFFICER	SHERN, ROALD J
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

FLUORIDE UPTAKE IN TOOTH ENAMEL

OBJECTIVES AND WORK SCOPE

Contractor shall provide all necessary staff, facilities, and populations to carry on a field trial of a topical fluoride study to: Assess the level of enamel fluoride attained after a series of treatments of topical gel to teeth of children consuming fluoride deficient water; Assess the rate of loss of fluoride from enamel after treatments have been completed; and Assess the residual anti-caries effect of three short treatment regimens.

SALIENT RESULTS TO DATE

The examinations of 650 students and the biopsy of 170 student subsample was conducted in February, 1973, as contracted. The data shows no definitive results for either response. However, a mean reduction in caries in the drug-treated groups suggests that a second year will demonstrate some drug efficacy.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22401-03
ORGANIZATION	PENNSYLVANIA STATE UNIVERSITY
ADDRESS	UNIVERSITY PARK PA
INITIAL START DATE	02-27-72
EXPIRATION DATE	02-26-76
ORGANIZATION CODE	INT
PROJECT DIRECTOR	MUNGER, BRYCE L
NIDR PROJECT OFFICER	BOSMA, JAMES F
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

STUDY OF DEVELOPMENT OF ORAL SENSORY RECEPTORS

OBJECTIVES AND WORK SCOPE

The Contractor shall continue to select and breed monkeys, obtain fetuses at selected gestational age, and prepare specifically studied areas for anatomical evaluation by microscopic and ultramicroscopic methods. Contractor shall describe the histological progression of development as evidenced in the specimens prepared in this project. During this period of the project, cesarean section shall be performed upon approximately twenty tissue blocks for between 50 and 200 slides.

SALIENT RESULTS TO DATE

Most of the rhesus fetuses, neonates, postnatally maturing, and mature specimens have been obtained. Each has been prepared in a manner appropriate to light and electron microscopy. A few more specimens are needed to confirm variant or unexpected observations in certain areas, such as the lip. This material is under continued study by the Principal Investigator. His interest and expertise in oral area mucosal and skin receptors continue to accumulate. The developmental pattern of these receptors at standard sites on the lip, cheek, tongue, and palate is becoming apparent. This area accumulates concentrations of a remarkable variety of receptors, and it thus affords notable opportunities for histological study.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22402-03
ORGANIZATION	DUKE UNIVERSITY
ADDRESS	DURHAM NC
INITIAL START DATE	05-17-72
EXPIRATION DATE	11-16-75
ORGANIZATION CODE	INT
PROJECT DIRECTOR	DANIELS, CHARLES A
NIDR PROJECT OFFICER	NOTKINS, ABNER L
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

RHEUMATOID FACTOR AND INFECTIOUS ANTIBODY COMPLEXES

OBJECTIVES AND WORK SCOPE

The contractor proposes to test the ability of different concentrations of rheumatoid factor, complement, rheumatoid factor plus complement, Ctg and cryoglobulins to neutralize infectious virus-antibody complexes. Herpes simplex, vaccinia influenza and hepatitus virus will serve as models. Fixation of complement by the alternate pathway and lysis of sensitized virus by complement also will be studied.

SALIENT RESULTS TO DATE

During the first year of the contract, Dr. Daniels showed that earlier studies with herpes simplex virus and rheumatoid factor could be repeated with vaccinia virus indicating the general nature of the phenomenon. In the second year, he showed that rheumatoid factor was present in over 50% of the sera obtained from patients with hepatitis B virus antigenemia and that rheumatoid factor could interact with hepatitis B antigen-antibody complexes. In addition, he demonstrated that neutralization of herpes simplex virus and the destruction of herpes simplex virus-infected cells by antiviral antibody and complement could be accomplished for more effectively by the classic rather than the alternate complement pathway. Last year, Dr. Daniels showed the high concentrations of herpes simplex virus were shed from the lesions of patients with recurrent herpes labialis and that the virus existed in the form of an infectious virus antibody complex. It was concluded that patients with active lesions shed virus for a number of days and that in nature, infection may be transmitted in the form of an infectious virus-antibody complex.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22403-02
ORGANIZATION	UNIVERSITY OF ALABAMA
ADDRESS	BIRMINGHAM AL
INITIAL START DATE	06-05-72
EXPIRATION DATE	12-04-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	NAVIA, JUAN M
NIDR PROJECT OFFICER	ROGERS, WILLIAM E
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

DEVELOPMENT SUGAR-SUBSTITUTED FOODS LOW CARIES POTENTIAL

OBJECTIVES AND WORK SCOPE

The Contractor shall formulate, manufacture, and test in the laboratory a group of snack foods which have been modified by substitution of the sucrose with other carbohydrates to reduce its caries promoting properties. Specifically, the Contractor shall: Evaluate by conventional rat caries tests the relative cariogenicity of various sweetening agents when substituted for various levels of sucrose in the diet; Design and develop taste-acceptable (to humans) snack foods and desserts which would contain sucrose substituted sweetening agents of low cariogenicity to the rat; and Test for cariogenicity (in rats) snack foods in which low cariogenic sweetening agents have been used.

SALIENT RESULTS TO DATE

Development of the rat assay: The second Konig Feeder has just been received. Food consumption and body weight gain data has been obtained using the old feeder. Evaluation of the caries potential of several carbohydrates: Fourteen carbohydrates have been tested for caries promotion in four large ad lib feeding experiments. These experiments show Buccal Scores ranging from 6 (pectin) to 15 (sucrose) and 18 (B lactose). Interestingly, fructose was 15, glucose 13, and dextran 11. A series that was generally similar was obtained for Sulcal Scores. Cariogenic properties largely parallel the sweetness of the carbohydrates. Some results show that combinations of carbohydrates have lower caries promoting capacity than the individual sugars at lower concentration. Formulation of acceptable snack foods: Caramel candy, sugar cookies, and oatmeal cookies have been developed that pass a flavor test and that have reduced levels of sucrose, typically 15% of customary. Development of successful formulas appear to have been acienved with difficulty. Low sucrose puddings also have been prepared. The caries-promoting activity of certain of these snacks now is being assayed. Objectives of workscope are closely followed.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22404-02
ORGANIZATION	UNIVERSITY OF FLORIDA
ADDRESS	GAINESVILLE FL
INITIAL START DATE	05-16-72
EXPIRATION DATE	08-31-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	OLSON, GERALD A
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

STUDY OF CARIES-INHIBITORY ACTIVITY IN HUMAN SALIVA

OBJECTIVES AND WORK SCOPE

The Contractor shall investigate the existence and delineate the prevalence of naturally occurring caries inhibitory factors in human saliva. Specifically, he shall perform the following: Saliva shall be collected from at least 100 subjects; Information relative to caries experience shall be recorded for each human subject which shall include oral examinations for DMFT, and other pertinent data as required for clinical evaluation of present and past caries activity; All saliva samples shall be subjected to quantitative in vitro assay for adherence inhibitory activity of saliva as tested against at least six strains of Streptococcus mutans.

SALIENT RESULTS TO DATE

Over sixty human saliva samples have been assayed for their adherence inhibitory activity (AID). An apparent trend exists between higher AIA and lower DMFT scores. However, the converse relationship lacks validity. Statistical ana lyses comparing fewer variables may serve to clarify this somewhat muddied picture. Some characteristics of the sali vary factor are; non-dialyzability; heat stability at 56 degrees C; and selective inhibition of certain mutans strains. Further characterization of the factor will be done. Extensions of the use of several mutans strains in the AIA has uncovered new cross-relationships. Shared antigens between some mutans strains have been recognized by the use of S. mutans antisera in the AIA. Inhibition of dextran-sucrose-induced agglutination appears to correlate with AIA relationships. However, antibody to glucosyltransferase indicates immunologic identity in the AIA but diversity in the agglutination-inhibition test. Further work on these relationships should increase our knowledge of strain diversity and the role of transferases within the mutans group.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22406-01
ORGANIZATION	RESEARCH FOUNDATION OF SUNY
ADDRESS	ALBANY NY
INITIAL START DATE	06-12-72
EXPIRATION DATE	08-31-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	FISCHMAN, STUART L
NIDR PROJECT OFFICER	SUOMI, JOHN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

DEGREE OF EFFECTIVENESS OF CARIES PREVENTIVE PROCEDURES

OBJECTIVES AND WORK SCOPE

Effectiveness of a combined series of caries-preventive measures will be evaluated in 1500 students (6-7-8th grades) in Buffalo, New York. All will undergo standard preventive measures: fluoridated drinking water, restorative dental care, oral hygiene instruction, and prophylactic treatment. Additionally, Test Groups will get adhesive sealant applied to pit and fissure tooth areas followed by topical application of acidulated fluoride phosphate solution. One Test Group will also be given special oral hygiene instruction and unusual encouragement to seek appropriate dental care; selected individuals, moreover, will receive specific behavioral procedures designed to emphasize motivational incentives to change oral hygiene behavior.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22407-03
ORGANIZATION	UNIVERSITY OF MINNESOTA
ADDRESS	MINNEAPOLIS MN
INITIAL START DATE	05-02-72
EXPIRATION DATE	11-01-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	LILJEMARK, WILLIAM F
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

AGENTS AFFECTING ADHERENCE OF CARIOGENIC MICROORGANISMS

OBJECTIVES AND WORK SCOPE

The Contractor shall perform the following efforts: (1) Isolate and characterize the "fuzzy coats" of Streptococcus salivarius, Streptococcus sanguis, Streptococcus miteor, and Streptoccocus mutans. (2) Use appropriate radiostopic tags to isolate and characterize the soluble and insoluble dextrans from the same organisms. (3) Utilize the "fuzzy coats", radiolabeled dextrans, and radiolabeled bacteria to analyze the site-specific interactions which result in the selective adherence of oral streptococci to enamel powder and hydroxyapatite. (4) Analyze the effectiveness of a variety of agents including polysacchaharases, proteases, lipases, low molecular weight dextrans, and detergents which might inhibity the development of sucrose-caused plaque by blocking specific sites of the components involved in adherence.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22410-02
ORGANIZATION	UNIVERSITY OF MICHIGAN
ADDRESS	ANN ARBOR MI
INITIAL START DATE	06-30-72
EXPIRATION DATE	06-30-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BAGRAMIAM, ROBERT A
NIDR PROJECT OFFICER	DRISCOLL, WILLIAM S
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

A COMBINED SERIES OF CARIES PREVENTIVE PROCEDURES

OBJECTIVES AND WORK SCOPE

The Contractor shall complete a three year study to determine the degree of effectiveness of a combination of several caries-preventive measures in a population of children in a Michigan community. A total of 1200 students shall be selected from elementary schools in the optimally fluoridated city of Ypsilanti by utilizing 600 each from Grades 1 and 6. At various intervals of time the children will receive prophylaxis, application of adhesive sealants, application of phosphate-fluoride gel, oral hygiene education and technique instruction, and restorative dental care. Interim technical reports, summaries, and a final report is required.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22413-02
ORGANIZATION	UNIVERSITY OF PENNSYLVANIA
ADDRESS	PHILADELPHIA PA
INITIAL START DATE	06-29-72
EXPIRATION DATE	12-28-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	CAGAN, ROBERT H
NIDR PROJECT OFFICER	ROUSSOS, GERASSIMOS
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

EVALUATION OF THE SWEET-TASTING PROTEIN MONELLIN

OBJECTIVES AND WORK SCOPE

Conduct studies to biochemically characterize a sweet-tasting protein (Monellin) which has been isolated from the berries of a tropical plant, Dioscoreophyllum cumminsii, as possible application as a substitute for sucrose, particularly in snack-type foods. Contractor shall isolate the protein, determine the molecular weight and isoelectric point, ascertain the UV and fluorescent spectra, determine the amino acid composition including cysteine, cystine, tryptophan, and amide moiety, and perform appropriate degradation studies.

SALIENT RESULTS TO DATE

The past year's performance of the Contractor was of high quality throughout and in accordance with both the scope and the timetable in the contract. Thus, he was able to confirm the presence of a single cysteine residue in the monellin molecule. Moreover, the sulfhydryl group was found to be not readily accessible to reaction with sulfhydryl reagents or oxidation by air and that it must be in the reduced form for the protein to taste sweet. Studies with protein denaturants have shown that monellin is more stable at acid pH than at neutral or alkaline pH and the pH during denaturation itself is critical to the subsequent recovery of sweetness, but the pH existing during renaturation has little influence on the recovery of sweetness. It was also found in these studies that aggregated denatured monellin has lost its titratable sulfhydryl and is not swee. Finally, preliminary studies have indicated that monellin in solution is fairly thermostable, retaining approximately 25% of its sweetness after heating in a boiling water-bath for fifteen minutes and have also suggested that fluorescence spectroscopy would be a sensitive and specific indicator of conformational changes in the protein molecule which accompany changes in sweetness.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE22414-07
ORGANIZATION	LITTON BIONETICS, INC
ADDRESS	KENSINGTON MD
INITIAL START DATE	06-30-72
EXPIRATION DATE	09-29-75
ORGANIZATION CODE	INT
PROJECT DIRECTOR	MC COY, JAMES
NIDR PROJECT OFFICER	MERGENHAGEN, STEPHAN
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

ISOLATION & CHARACTERIZATION ANTIGENS FROM HUMAN PLAQUE

OBJECTIVES AND WORK SCOPE

Independently, and not as an agent of the Government, the Contractor shall exert its best efforts to conduct studies, as necessary, to isolate and identify antigens in human dental plaque which have the potential to transform lympho cytes from patients with periodontal disease and to characterize biologically-active effector molecules such as lymphotoxin and bone resorbing factors, produced in tissue culture cell lines or by lymphocytes when stimulated by plaquederived or other antigens or mitogens.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE22415-01
ORGANIZATION	UNIVERSITY OF MINNESOTA
ADDRESS	MINNEAPOLIS MN
INITIAL START DATE	06-29-72
EXPIRATION DATE	01-31-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	LILJEMARK, WILLIAM F
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

STREP & POLYSACCHARIDE FORMING ABILITY OF DENTAL PLAQUE

OBJECTIVES AND WORK SCOPE

The major purpose of this research is to evaluate specific microorganisms and sucrose activity of plaque samples as an indicator of future caries potential.

SALIENT RESULTS TO DATE

The study is progressing as outlined in the original contract proposal. The polysaccharid forming ability of dental plaque as quantitated by our method was not significantly associated with caries prevalence. The relative percentages of S. mutans and lactobacilli were the only microorganisms to show significant positive association with caries prevalence. Together they explained nearly eight per cent of the variance in total caries prevalence. The second plaque sampling has been concluded with a loss of 14.5% of the subjects. This attrition was primarily due to changes in school boundaries. In addition to differentiating and quantitating the cariogenic microorganisms by colonial morphology a selective media for S. mutans and the quantitation of total plaque by turbidity has been added to the study protocol. The third plaque sampling will begin in March 1974. This phase in the study will provide information regarding one year incidence of caries. A summary of these findings as well as changes in oral micoorganisms at six month intervals will be available in the January, 1975 progress report and summary.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE32405-01
ORGANIZATION	CENTRAL INSTITUTE FOR EXPERIMENTAL ANIMALS
ADDRESS	TOKYO, JAPAN
INITIAL START DATE	09-14-72
EXPIRATION DATE	09-13-74
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	NISHIMURA, HIDEO
NIDR PROJECT OFFICER	CHRISTIANSEN, R L
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

PRENATAL DEVELOPMENT OF HUMAN ORAL AND FACIAL STRUCTURES

OBJECTIVES AND WORK SCOPE

A Manuscript entitled "Prenatal Development of the Human with Specific Reference to Oral-Facial Structures" is aimed at publication of a monograph under the authorship of Dr. Hideo Nishimura on complete descriptive study of the normal and abnormal development of human embryo and fetus with special reference to the head and oral-facial complex. This will furnish dentists, oral surgeons, and other biomedical scientists with the most reliable standard for their studies on the related subjects. The manuscript will be for disposition by the National Institute of Dental Research.

SALIENT RESULTS TO DATE

The Principal Investigator and his group collected 1,335 human embryonic and 202 fetal specimens and those were added to his collection obtained so far. By using a number of normal embryonic and fetal specimans (stage: 2mm = 35cm in CR length) selected from the collection, various developmental features of the oral-facial and related structures were photographed. Items of the prepared serial pictures and their numbers are as follows: lateral view of the whole body, 20; front view of the face, 20; oblique view of the face, 12; view of the branchial arches, 9; view of the optic region, 4; view of the lip, 5; view of the gum, 3; and view of the roof of the oral cavity, 7. Among the above pictures, those at the early embryonic stage are especially valuable in terms of that those have never been prepared elsewhere.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32408-01
ORGANIZATION	ROYAL COLLEGE OF SURGEONS OF ENGLAND
ADDRESS	LONDON, ENGLAND
INITIAL START DATE	12-04-72
EXPIRATION DATE	12-03-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	COLE, MICHAEL F
NIDR PROJECT OFFICER	LARSON, RACHEL H
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

STUDY OF EFFECT OF DIETARY ADDITIVES ON PLAQUES & CARIES

OBJECTIVES AND WORK SCOPE

Plaque chemistry and caries incidence will be determined in 12-16 month old monkeys maintained on a cariogenic diet, with and without supplements of potential anti-cariogenic substances: pyridoxine and sodium inositol phosphate. Plaque samples obtained before and during the feeding experiments will be examined for numbers of microorganisms producing extracellular and intracellular polysaccharides, and also for the quantities of calcium phosphorus, magnesium, carbohydrate, and protein. The identity of the acids produced in situ by plaque from sugars in the different diets will be determined.

SALIENT RESULTS TO DATE

Progress on this contract during the past year has been in keeping with the proposed schedule. A larger group of monkeys has been brought in from the wild, subjected to testing and treatment after which 24 of the most desirable were selected and set up in the three experimental groups. The necessary equipment for assays has been purchased or assembled, including installation and calibration when needed. Test procedures have been selected, modified where necessary, and reliability established. Both baseline and early experimental data have been collected and the whole study appears to the project officer to be off to an excellent start.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32417-03
ORGANIZATION	LITTON BIONETICS, INC
ADDRESS	ROCKVILLE MD
INITIAL START DATE	04-22-73
EXPIRATION DATE	08-31-75
ORGANIZATION CODE	INT
PROJECT DIRECTOR	DOREY, C KATHLEEN
NIDR PROJECT OFFICER	HAND, ARTHUR R
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

EM HYDROLYTIC ENZYMES IN PERIO LIGAMENT OF RAT

OBJECTIVES AND WORK SCOPE

The Contractor shall conduct studies and investigations, as necessary, to provide suitable tissue preparation and staining techniques for the ultrastructural localization of the following enzyme activities in mineralized tissues of the rat jaw: Aryl sulfatase, 5'-Nucleotidase, Thiamine pyrophosphatase, and N-acetylglucosaminidase. Techniques shall also be presented for validating enzyme localization and identification of the associated cell types. The ultrastructural localization of such enzyme activities shall be consistent with the reported light microscope findings.

SALIENT RESULTS TO DATE

The contractor has established considerable technical expertise in handling E.M. cytochemical preparations of the rat periodontal ligament. The studies of TPPase and aryl sulfatase localization are nearing completion and good progress has been made on the localization of NAGase activity. Technical difficulties have impeded progress with 5' -nucleotidase. Intense aryl sulfatase activity has been confirmed in the perivascular cells, and in osteoclasts. TPPase has also been localized to osteoclasts, but most of the activity appears to be lysosomal, which may indicate the neutral tail of activity of a non-specific acid phosphatase. TPPase is also associated with intracellular collagen fibrils and with extracellular collagen in certain areas. NAGase activity has been localized in the lysosomes of osteoclasts and perivascular cells, and in the Golgi of osteoblasts and the ER of certain fibroblasts.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32418-01
ORGANIZATION	NEW YORK MEDICAL COLLEGE
ADDRESS	NEW YORK NY
INITIAL START DATE	04-16-73
EXPIRATION DATE	05-31-76
ORGANIZATION CODE	INT
PROJECT DIRECTOR	PULLMAN, IRA
NIDR PROJECT OFFICER	FOWLER, BRUCE O
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

APATITIC CRYSTALS AND MINERAL-PROTEIN COMPLEXES

OBJECTIVES AND WORK SCOPE

The contractor shall conduct electron paramagnetic resonance studies of apatite structure and mineral-matrix bonding to include a series of synthetic as well as biological apatite samples and specimens. These shall be irradiated and examined in order to characterize the free radical species produced and to interpret same in terms of their molecular structural environments, Such studies are also to include a series of calcium phosphate macromolecule complexes which are to be examined by spin probe and spin transfer procedures. The purpose of these experiments is to establish chemical bonding sites between molecule and macromolecule in each complex. The results of same will be reported as the work progresses.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32419-01
ORGANIZATION	AMERICAN DENTAL ASSOCIATION
ADDRESS	CHICAGO IL
INITIAL START DATE	04-30-73
EXPIRATION DATE	04-29-75
ORGANIZATION CODE	INT
PROJECT DIRECTOR	STEFFEK, ANTHONY J
NIDR PROJECT OFFICER	JOHNSTON, MALCOLM C
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

ELECTRON MICROSCOPY OF MIGRATING EMBRYONIC CELLS

OBJECTIVES AND WORK SCOPE

The technique of steroscan electron microsopy has been utilized by our division in an attempt to complement current techniques in describing facial formation and has greatly facilitated the assessment of facial development both at the early and later stages of development. The objectives of the present proposal are to extend our initial experiments in characterizing the early morphogenesis of neural crest migration with steroscan electron microscopy.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32420-01
ORGANIZATION	CLEMSON UNIVERSITY
ADDRESS	CLEMSON SC
INITIAL START DATE	05-01-73
EXPIRATION DATE	05-01-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	KLAWITTER, JEROME J
NIDR PROJECT OFFICER	VALEGA, THOMAS M
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

HISTOLOGICAL ACCEPTANCE OF ARTIFICALLY FABRICATED TEETH

OBJECTIVES AND WORK SCOPE

Incisor shaped teeth fabricated from a crome cobalt alloy, poly-methylmethacrylate, and ceramic materials will be im planted into the jaws of dogs to determine the histological acceptance of artificially fabricated teeth of different material composition in animals. Samples of the materials will be submitted to routine toxicology assay and to characterization studies. Artificial teeth will be stabilized for a period of two months. Clinical evaluation and radiographic evaluation of the artificial teeth will be performed after implant time periods ranging from one month. Tissue blocks containing implanted teeth will be removed periodically to assess response at the microscopic level. Sufficient teeth will be implanted to permit statistically valid conclusions as to the histological acceptance of each material.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32421-01
ORGANIZATION	UNIVERSITY OF FLORIDA
ADDRESS	GAINESVILLE FL
INITIAL START DATE	05-07-73
EXPIRATION DATE	05-01-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	STANLEY, HAROLD R
NIDR PROJECT OFFICER	VALEGA, THOMAS M
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

HISTOLOGICAL ACCEPTANCE OF ARTIFICALLY FABRICATED TEETH

OBJECTIVES AND WORK SCOPE

Conduct a study to determine the histological acceptance of artificially fabricated teeth made from the following materials: poly-methylmethacrylate, a crome cobalt alloy, and a ceramic or bioglass-ceramic. Artificial incisor teeth will contain a porous coating of the same material used in preparing the solid portion of the root and will be implanted in baboons. Samples of the materials will be submitted to routine toxicology assay and to characterization studies. Artificial teeth will be implanted into the natural socket in baboons and will be stabilized for a period of three months. Clinical and radiographic evaluation of the artificial teeth will be performed after implants have been in place for more than one month. Tissue blocks will be removed to assess response at microscopic level. Sufficient teeth will be implanted to permit statistically valid conclusions as to the histological acceptance of each material.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32422-01
ORGANIZATION	HARVARD UNIVERSITY
ADDRESS	CAMBRIDGE MA
INITIAL START DATE	05-18-73
EXPIRATION DATE	05-17-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	SHULMAN, LEONARD B
NIDR PROJECT OFFICER	VALEGA, THOMAS M
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

A STUDY OF ARTIFICIAL TEETH

OBJECTIVES AND WORK SCOPE

The Contractor shall exert his best efforts to determine the histologic acceptance of teeth artificially fabricated from the polymer of reagent grade methylmethacrylate, formed in a variety of "root" designs and implanted into the jaws of baboons. Specifically, the Contractor shall: Select representative incisor shaped teeth fabricated in the following rooth forms natural tooth replica, preformed natural tooth, and blades; Determine the effect on acceptability of smooth versus porous root survaces and also the effects of preparing the root surface with slots and grooves; Perform clinical evaluation and radiographic evaluation of the artificial teeth after implant time periods ranging from one (1) week; Remove tissue blocks containing the implanted teeth periodically to assess response at the microscopic level. Sufficient teeth shall be implanted to permit statistically valid conclusions as to the biological and clinical acceptance of each design. SALIENT RESULTS TO DATE

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32423-04
ORGANIZATION	AMERICAN DENTAL ASSOCIATION
ADDRESS	CHICAGO IL
INITIAL START DATE	05-22-73
EXPIRATION DATE	05-22-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	GIFT, HELEN C
NIDR PROJECT OFFICER	FREW, RALPH A
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

STUDY OF METHODS OF DELIVERING CARIES PREVENTION

OBJECTIVES AND WORK SCOPE

The Contractor will assess the knowlege, beliefs, attitudes, and current actions of practicing dentists relative to procedures for the prevention of dental caries. Additionally, the Contractor shall determine the potential of the preventive dentistry activities of the current delivery system for participation in a comprehensive caries prevention program for children. Finally, the Contractor shall design a study for determining the effectiveness of the dentist, singley and as a member of professional societies, in changing public attitudes and behavior relative to caries preventive measures. For the purpose of this contract, technics and agents to be considered as caries prevention shall be limited to fluoride therapy (exclusive of water fluoridation), adhesive pit and fissure sealants, personal oral hygiene education, and diet counseling.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32424-01
ORGANIZATION	UNIVERSITY OF CALIFORNIA
ADDRESS	SAN FRANCISCO CA
INITIAL START DATE	06-22-73
EXPIRATION DATE	12-31-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	SILVERSTEIN, STEVEN
NIDR PROJECT OFFICER	MEYERS, RHEA
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

STUDY OF EFFECT OF DAILY SUPERVISED DEPLAQUING OF TEETH

OBJECTIVES AND WORK SCOPE

From a population of 600 children between the ages of 12 and 13 years who possess a relatively high level of dental caries and gingivitis, establish one test and one control group of sufficient size to ascertain if there is a statistical difference between the test and control groups. Record dental caries for each tooth one every year. Gingival inflammation and plaque scores shall be recorded every three months. Oral hygiene procedures by the test group shall keep the tooth surface free from plaque. Wax-Flossing, brushing, and disclosing solutions shall be conducted daily by the participants under the direct supervision of the Contractor to insure the removal of visual plaque deposits. A combination of group and individual instruction along with periodic review sessions shall teach the test group the performance effective oral hygiene procedures. Analyze data.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE32425-01
ORGANIZATION	GULF SOUTH RESEARCH INSTITUTE
ADDRESS	NEW ORLEANS LA
INITIAL START DATE	06-29-73
EXPIRATION DATE	08-28-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	RAWLS, HENRY R
NIDR PROJECT OFFICER	FREW, RALPH A
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

DIAGNOSTIC SYSTEM FOR EARLY DETECTION OF DENTAL CARIES

OBJECTIVES AND WORK SCOPE

The contractor shall exercise its best efforts in the conduct of research studies directed toward the formulation and development of a fluorescent dye penetration technique intended for the early detection of dental caries by human observers. Develop non-proprietary dye formulations which shall be evaluated in various penetrant vehicles. Conduct toxicological testing. Conduct psychophysical evaluation. Determine the convenience factors and esthetics from the results of experiments designed to test the applicability of various formulations. The results of these evaluations shall be available within ten months to permit adequate time for compilation of findings and recommendations including necessary approvals for possible in vivo study involving human volunteers. The Contractor shall submit the selected dye to the Federal Drug Administration for approval in use in clinical trials.

SALIENT RESULTS TO DATE

Three candidate formulas for use as caries-disclosing fluids have been tested to determine their toxicological properties, their mucous-membrane irritation potential, and their ability to enhance the detectability of early-caries like-lesions. The flourescent "active ingredients" of the three formulas were found to have no pathological effect in either rats or beagle dogs and did not have any signs of eye irritation in rabbits. Psychophysical testing of the three candidate formulas in vitro revealed statistically significant differences in lesion-disclosing performance among the formulas as compared to conventional examination methods. Progress was made in preparing IND applications for FDA, and an instrument for ultraviolet fluorescence oral examinations has been designed. The lesion-disclosing performance was limited to the detection of lesions produced by acid etching when the examiners were aware that the probability of a surface having a lesion was one in two. Performance on naturally occurring lesions was less dramattic, and reports on validity estimates with hardness as the criteria was limited to etched areas.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32427-03
ORGANIZATION	STATE OF FLORIDA - DIVISION OF HEALTH
ADDRESS	JACKSONVILLE FL
INITIAL START DATE	06-29-73
EXPIRATION DATE	09-30-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	RINGELBERG, MEL
NIDR PROJECT OFFICER	DRISCOLL, WILLIAM S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

TEST OF EFFICACY OF AMINE FLUORIDE MOUTHRINSE

OBJECTIVES AND WORK SCOPE

The purpose of this study is to determine the caries-preventive effects and the effects on dental plaque and gingivitis of an amine fluoride mouthrinse and dentifrice, when used alone and when used in combination with one another. The investigation shall also compare the effects of the amine fluoride products with their respective inorganic counterparts. The starting population shall comprise 2000 children attending the sixth grades of middle schools in the nonfluoridated area of Escambia County, Florida. Each child will rinse daily with a fluoride or non-fluoride mouthwash under supervision at school, and brush daily with a fluoride or non-fluoride toothpaste without supervision at home.

SALIENT RESULTS TO DATE

A clinical trial to test the efficacy of an amine fluoride mouthrinse and dentifrice with their inorganic counterparts was undertaken in Pensacole, Florida. Six treatment groups and a control were used. The treatment groups used either an amine fluoride dentifrice containing 1,250 p.p.m. F ad libritum at home and an amine fluoride mouthrinse containing 250 p.p.m. F daily at school or a stannous fluoride-calcium pyrophosphate dentifrice (1000 p.p.m.F) ad libritum at home and a sodium fluoride (250 p.p.m.F) rinse daily at school. The products were used separately and in combination with appropriate matching high placebos. 2,047 caries, plaque, and gingival baseline examinations were done. Plaque and gingival exams were subsequently done on a 50% sample of the participants at 12 and 20 week intervals after initiation of the mouthrinse procedure. No treatment effects were apparent from the plaque and gingiva exams, although an overall reduction in the index scores was shown. 1,647 caries examinations were completed and analysis of this data is being performed.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32428-01
ORGANIZATION	AMERICAN DENTAL ASSOCIATION
ADDRESS	CHICAGO IL
INITIAL START DATE	08-01-73
EXPIRATION DATE	07-31-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	HEFFERREN, JOHN J
NIDR PROJECT OFFICER	KORTS, DAVID C
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

ETCH BIOPSY DETERMINING FLUORIDE CONTENT OF TOOTH ENAMEL

OBJECTIVES AND WORK SCOPE

The objective of this proposal is to develop methods to systematically delineate the precision and accuracy of the sampling and subsequent steps of an abrasive and an acid etch fluoride biopsy technique for estimating fluoride content in the outermost layers of tooth enamel which are applicable to field survey requirements.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32429-01
ORGANIZATION	UNIVERSITY OF IOWA
ADDRESS	IOWA CITY IA
INITIAL START DATE	08-01-73
EXPIRATION DATE	07-31-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	WEI, STEPHEN H
NIDR PROJECT OFFICER	KORTS, DAVID C
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

ETCH BIOPSY FOR DETERMINING FLUORIDE OF TOOTH ENAMEL

OBJECTIVES AND WORK SCOPE

The objective of this proposal is to develop methods to systematically delineate the precision and accuracy of the sampling and subsequent steps of an abrasive and an acid etch fluoride biopsy technique for estimating fluoride content in the outermost layers of tooth enamel which are applicable to field survey requirements.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE32430-01
ORGANIZATION	FORSYTH DENTAL CENTER
ADDRESS	BOSTON MA
INITIAL START DATE	06-29-73
EXPIRATION DATE	10-31-74
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	LOBENE, RALPH R
NIDR PROJECT OFFICER	SHERN, ROALD J
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

STUDY OF ANTIMICROBIAL AGENTS

OBJECTIVES AND WORK SCOPE

Perform a series of short-term (1-16 weeks) clinical trials of anti-microbial and anti-plaque agents, on groups of up to fifty subjects per trial. The agents to be tested will be selected, acquired, and furnished by the Government to the Contractor. The exact number of compounds to be tested is unknown; however, it is envisioned that ten study panels (up to fifty subjects each) will be required. Some study panels may be used more than once, and trials of several agents may take place simultaneously. It is expected that the populations utilized will be representative of school aged children and young adult males living in the area where the trials are conducted. Because of the small sample size to be studied, a low attrition rate is mandatory.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42431-02
ORGANIZATION	INSTITUTE FOR TECHNOLOGIC INVESTIGATIONS
ADDRESS	BOGATA, COLOMBIA
INITIAL START DATE	09-18-73
EXPIRATION DATE	06-15-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	MONCADA, FELIX
NIDR PROJECT OFFICER	CHASSEY, BRUCE
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

EXPERIMENTAL DEVELOPMENT OF INVERT PANELA

OBJECTIVES AND WORK SCOPE

The main objective of this research is the experimental development of invert panela for possible use in the uman diet. A successful invert panela must be similar in appearance, flavor, physical consistency, and acceptance to ordinary panela. Panela, incidently, is the solid product obtained from clarifying and concentrating sugar cane juice.

SALIENT RESULTS TO DATE

Progress has been very good even though goals were not fully meg (e.g., invert panela is not a reality). The project had two phases: to develop enzymatic inversion procedures (six months); and to develop and test the product. The first phase was completed earlier than expected. The second phase was organized to test the most economical and simplest procedures first, even if their chances of success were less than for more complicated techniques. It has become clear after exhaustive efforts by the IIT that more sophisticated techniques are required. At present a suitable product is available from the use of vacuum ovens (it had been hoped that vacuum techniques could be avoided). The exact conditions will soon be available so that the next six months can be used for testing and acceptability studies.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42434-01
ORGANIZATION	HAZELTON LABORATORIES INCORPORATED
ADDRESS	VIENNA VA
INITIAL START DATE	05-01-74
EXPIRATION DATE	09-30-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BOYD, DALE D
NIDR PROJECT OFFICER	BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

ANTI-CARIES IMMUNIZATION IN SUBHUMAN PRIMATES

OBJECTIVES AND WORK SCOPE

The Contractor will provide 40-50 Macaca fascicularis monkeys approximately sixteen months of age. The Contractor would house and maintain the monkeys with suitable sterility and safety procedures for a period of not less than two years. The monkeys would be fed eight times daily and less frequently on weekends with a special caries-conducive diet which would be specified by NIDR. The Contractor would also provide facilities for clinical (general anesthesia and minor oral surgery) and radiographic examinations.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42435-02
ORGANIZATION	SOUTHERN RESEARCH INSTITUTE
ADDRESS	BIRMINGHAM AL
INITIAL START DATE	05-15-74
EXPIRATION DATE	05-14-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	COWSAR, DONALD R
NIDR PROJECT OFFICER	PARAKKAL, PAUL
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

IMPROVED MATERIALS FOR MAXILLOFACIAL PROSTHESIS

OBJECTIVES AND WORK SCOPE

Complete developmental phase by determining stain resistance, wettability, cleanability, dimensional stability, opacity, and adhesion to tape and surgical adhesive; optimizing bulk viscosity, pot life, vulcanization time and temperature, mold release and shrinkage, and intrinsic and extrinsic coloration techniques; evaluating special techniques for fabricating hollow, foam-filled, or microballon-filled prostheses. Conduct pre-clinical phase by formulation of larger batches, determination of storage stability, and evaluation with animals of the dermal and ocular toxicity of the components of kits and the cured silphenylene elastomers. Conduct clinical phase by fabrication of custom prostheses for patients and follow-up by inspection, interview, and examination of patients & questionnaire of patient acceptance, wear characteristics, and shortcoming of the silphenylene prostheses.

SALIENT RESULTS TO DATE

The Contractor has synthesized the polymer, determined its basic mechanical properties, compared its properties to other maxillofacial materials currently used. They have found that silphenylene elastomer is stronger, tougher, softer, and more skin-like than silastic 399 which is the most commonly used extraoral maxillofacial prosthetic material. This material can be fabricated in stone molds at low temperatures. They have done preliminary work on colorability and development of coloration techniques and batch-to-batch reproducibility of the material. However, before siphenylene materials can be used clinically, they have to determine long term agining properties, strain resistance, wettability, cleanability, dimensional stability, opacity, and adhesion to tape and surgical adhesiveness and toxicity studies.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42436-02
ORGANIZATION	UNION CARBIDE CORPORATION
ADDRESS	BOUND BROOK NJ
INITIAL START DATE	06-01-74
EXPIRATION DATE	05-31-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	ROBESON, LLOYD M
NIDR PROJECT OFFICER	PARAKKAL, PAUL
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

IMPROVED MATERIALS FOR MAXILLOFACIAL PROSTHESIS

OBJECTIVES AND WORK SCOPE

Independently, and not as an agent of the Government, the Contractor shall exert his best efforts in the preparation of polymer derivatives that are non-toxic, non-allergenic, stain resistant, and with sufficient flexibility and color adaptability to be used as a technically reliable clinically acceptable extraoral maxillofacial prosthesis(i.e., artificial skin) in the facial regions of humans of different races and colors. The goal of the material development is to prepare a material which shall be: Capable of bing easily, reliably and inexpensively fabricated to various human facial shapes and roms and to various human racial colors and tones; applicable for clinical use and potentially acceptable to clinicians active in the area of rehabilitation; and capable of withstanding the stress of environmental sunlight, temperature and humidity without deterioration to the material's flexibility and color for a minimum of 2 years.

SALIENT RESULTS TO DATE

Work performed during first year is on schedule. Transfer of Kraton G to Roswell Park was delayed. Fabrication procedure for Kraton G which consists of solution coating the mold surface followed by foaming the Kraton G in mold under vacuum. Detailed weatherability studies have been completed on a series of materials. The thermoplastic polyurethanes exhibited poor weathering resistance given with the addition of UV stabilizers. The permanently plasticized PVC's showed better color retention than Mediplas combined with good property retention. The tetramethylcyclobutane (C-4) polycarbonate-siloxane block copolymer exhibited excellent weatherability. Synthesis work was initiated on silicone rubber block copolymers and polyester block copolymers. Fabrication studies are in progress on permanently plasticized PVC and will be started in the near future on the C-4 polycarbonate-siloxane block copolymers.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42437-02
ORGANIZATION	UNIVERSITY OF CONNECTICUT
ADDRESS	FARMINGTON CT
INITIAL START DATE	06-15-74
EXPIRATION DATE	06-14-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	TANZER, JASON M
NIDR PROJECT OFFICER	RIZZO, ANTHONY A
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

IN VITRO SCREENING OF CHEMICALS TO PREVENT PERIO PLAQUE

OBJECTIVES AND WORK SCOPE

The contractor will establish an in vitro plaque forming system to test a variety of agents for their potential to: prevent plaque formation; prevent plaque growth; and/or remove plaque. He will also determine the lowest effective concentrations of agents found active in the aforementioned tests. Five organisms, which are known to form plaque in vitro, are to be used in the test system, including Acetinomyces naeslundii, A. israleii, and A. viscosus as well as two chosen by the contractor.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42438-01
ORGANIZATION	FORSYTH DENTAL CENTER
ADDRESS	BOSTON MA
INITIAL START DATE	07-01-74
EXPIRATION DATE	06-30-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	TAUBMAN, MARTIN A
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

EFFICACY OF ANTIGENIC COMPONENTS IN ANTI CARIES VACCINES

OBJECTIVES AND WORK SCOPE

The Contractor shall investigate the effects of specifically induced salivary antibody to enzymes, enzyme fractions or enzyme-associated fractions of Streptococcus Mutans upon plaque bacteria and dental caries in pathogen-free and gnotobiotic rats and hamsters.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42439-04
ORGANIZATION	UNIVERSITY OF CALIFORNIA
ADDRESS	SAN FRANCISCO CA
INITIAL START DATE	06-28-74
EXPIRATION DATE	09-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	WYCOFF, SAMUEL J
NIDR PROJECT OFFICER	ROUSSOS, GERASSIMOS
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

EFFECT OF MOUTHRINSES CONTAINING CALCIUM GLYCERAPHOSPHATE

OBJECTIVES AND WORK SCOPE

The contractor will conduct a research study to determine the effect of mouthrinses containing calcium glycerophosphate on the chemical composition and development of plaque un humans.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42440-02
ORGANIZATION	NEW YORK STATE UNIVERSITY
ADDRESS	ALBANY NY
INITIAL START DATE	06-15-74
EXPIRATION DATE	06-14-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	GENCO, ROBERT J
NIDR PROJECT OFFICER	RIZZO, ANTHONY A
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

IN VITRO SCREENING OF CHEMICALS TO PREVENT PERIO PLAQUE

OBJECTIVES AND WORK SCOPE

The contractor will establish an in vitro plaque forming system to test a variety of agents for their potential to: provent plaque fromation; prevent plaque growth; and/or remove plaque. He will also determine the lowest effective concentrations of agents found active in the aforementioned tests. Five organisms, which are known to form plaque in vitro, are to be used in the test system, including Actinomyces naeslundii, A. israelii, and A. viscosus as well as two chosen by the contractor.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42441-01
ORGANIZATION	UNIVERSITY OF IOWA
ADDRESS	IOWA CITY IA
INITIAL START DATE	07-01-74
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	MACKENZIE, IAN C
NIDR PROJECT OFFICER	FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

DETERMINATION ROLE NUTRITION EPITHELIUM ORAL MUCOUS

OBJECTIVES AND WORK SCOPE

The objective of this research project is to determine the influence of protein, calorie, and vitamin deficiencies on oral mucous membranes in experimental animal model systems. Comparisons will be made between undernourished animals and those maintained on normal diets to determine the separate effects of chronic, progressive protein, calorie and vitamin deficiency on the health of the oral tissues. Tests conducted on the oral tissues of 3-4 year old Rhesus monkeys will determine; cell turnover rates; level of keratinization in deratinizing epithelium; degree of alteration of metabolic process (enzyme systems or protein synthsis); and studies of basement membranes of the various epithelial linings.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42442-01
ORGANIZATION	UNIVERSITY OF WASHINGTON
ADDRESS	SEATTLE WA
INITIAL START DATE	07-01-74
EXPIRATION DATE	05-31-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	ENWONWU, CYRIL
NIDR PROJECT OFFICER	FRAZIER, PAUL D
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

DETERMINATION ROLE NUTRITION EPITHELIUM ORAL MUCOUS

OBJECTIVES AND WORK SCOPE

The objective of this research projects is to determine the influence of protein, calorie, and vitamin deficiencies on oral mucous membranes in experimental animal model systems. Comparisons will be made between undernourished animals and those maintained on normal diets to determine the separate effects of chronic, progressive protein, calorie and vitamin deficiency on the health of the oral tissues. Tests conducted on the oral tissues of 3-4 year old Rhesus monkeys will determine (1) cell turnover rates, (2) level of keratinization in keratinizing epithelium, (3) degree of alteration of metabolic process (enzyme systems or protein synthesis), and (4) studies of basement membranes of the various epithelial linings.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	NO1 DE42443-01
ORGANIZATION	UNIVERSITY OF MICHIGAN
ADDRESS	ANN ARBOR MI
INITIAL START DATE	06-28-74
EXPIRATION DATE	06-27-77
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	GRAVES, RICHARD C
NIDR PROJECT OFFICER	DRISCOLL, WILLIAM S
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

TITANIUM TETRA & ACIDULATED PHOSPHATE FLUORIDE CARIES

OBJECTIVES AND WORK SCOPE

The proposed trial is double-blinded and involves children 11-12 years of age who shall be assigned randomly to two test groups (TiF4 and APF) and one placebo-control group. The selected study site must be stable, have a high prevalence of dental caries, have less than 0.4 ppm F in the drinking water and have a low level of dental care. The sample size will be estimated according to the increment of dental caries in that particular population, the variance, the expected magnitude of the difference, and the attrition rate. Treatments are to be given at the initiation of the study and every six months thereafter for a period of two years. DMFS clinical data will be obtained immediately prior to initiation of treatments, and at 12 and 24 month intervals.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42444-01
ORGANIZATION	UNIVERSITY OF OREGON
ADDRESS	PORTLAND OR
INITIAL START DATE	06-28-74
EXPIRATION DATE	05-31-78
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	LU, KUO H
NIDR PROJECT OFFICER	BRUNELLE, JANET
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

EFFECT OF SPECIFIC METHODS OF FLUORIDE ADMIN ON CONTROLLING CARIES

OBJECTIVES AND WORK SCOPE

This is a clinical trial designed to determine whether high-level, short-term application of fluoride is more efficacious than a low-level, long-term method. A comparison will be made between five-minute applications of acidulated phosphate fluoride gel (1.23% F) in custom-fitted trays for 10 consecutive school days under dental hygienist supervision and a one-minute use of fluoride mouthrinse (0.023% F) each school day for the duration of two school years. The comparative effectiveness of these two modes of application would be determined by the dental caries experience of study subjects.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42445-01
ORGANIZATION	FORSYTH DENTAL CENTER
ADDRESS	BOSTON MA
INITIAL START DATE	06-16-74
EXPIRATION DATE	06-15-78
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DE PAOLA, PAUL F
NIDR PROJECT OFFICER	HEIFETZ, STANLEY B
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

HIGH & LOW, SHORT & LONG TERM FLUORIDE TO CONTROL CARIES

OBJECTIVES AND WORK SCOPE

This is a clinical trial designed to determine whether high-level, short-term application of fluoride is more efficacious than a low-level, long-term method. A comparison will be made between five minute applications of acidulated phosphate fluoride gel (1.23% F) in custon-fitted trais for ten consecutive school days under dental hygienists' supervision and a one-minute use of fluoride mouthrinse (0.023% F) each school day for the duration of two school years. The comparative effectiveness of these two modes of application would be determined by the dental caries experience of study subjects.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE42446-02
ORGANIZATION	SOUTHERN RESEARCH INSTITUTE
ADDRESS	BIRMINGHAM AL
INITIAL START DATE	06-28-74
EXPIRATION DATE	06-27-77
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	COWSAR, DONALD R
NIDR PROJECT OFFICER	MIRTH, DALE B
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

FLUORIDE RELEASING SYSTEM FOR PROLONGED ORAL USE

OBJECTIVES AND WORK SCOPE

The objective of this research project is to develop a fluoride-containing material that: will release fluoride at a constant predetermined linear rate for a period of at least six months without maintenence or adjustment; can be easily applied or attached in the mouth (attachment to a tooth or teeth by adhesive or orthodontic bands, or as part of a space maintainer, or a simple adhesive coating); can be completely and safely removed at any time; and should contain materials that exhibit a very low order of toxicity in animals, are harmless to the teeth and harmless to and nonabsorbable through the oral and gastrointestinal mucoas.

SALIENT RESULTS TO DATE

Prototype devices have been prepared from copolymers of hydroxyethyl methacrylate and methyl methacrylate in the form of trilaminate discs and ribbons which release fluoride at a nearly constant rate into water, synthetic saliva, and human saliva under in vitro conditions. Work is currently in progress on determining the permeability parameters for sodium fluoride in the copolymer systems in the presence of saliva. These data should allow the contractor to refine the geometrical parameters and to fabricate final prototype devices with the desired release rates by the end of the developmental phase. Preliminary testing of mcehanical properties of the prototype devices has shown that appropriate copolymer ratios are fairly resistant to mechanical stresses expected to be encountered in the oral environment. A preliminary in vivo evaluation of the fluoride releasing system will be made in beagle dogs; if this evaluation shows the system will function properly under in vivo conditions, the more extensive in vivo evaluations proposed for the toxicity testing phase will be initiated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52447-01
ORGANIZATION	POLYSCIENCES, INCORPORATED
ADDRESS	WARRINGTON PA
INITIAL START DATE	08-01-74
EXPIRATION DATE	07-31-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	HALPERN, B DAVID
NIDR PROJECT OFFICER	MIRTH, DALE B
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

FLUORIDE RELEASING SYSTEM FOR PROLONGED ORAL USE

OBJECTIVES AND WORK SCOPE

The objective of this research project is to develop a fluoride-containing material the will; release fluoride at a constant predetermined linear rate for a period of at least six monts without maintenance or adjustment; can be easily applied or attached in the mouth (attachment to a tooth or teeth by adhesive or orthodontic bands, or as part of a space maintainer, or a simple adhesive coating); can be completely and safely removed at any time; and should contain materials that exhibit a very low order of toxicity in animales, are harmless to the teeth and harmless to and non-absorable through the oral and gastrointestinal mucosa.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52448-01
ORGANIZATION	ABCOR, INC
ADDRESS	CAMBRIDGE MA
INITIAL START DATE	02-15-75
EXPIRATION DATE	02-14-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	WILLIAMS, DAVID L
NIDR PROJECT OFFICER	BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

APPLICATION OF CARIOSTATIC AGENTS TO THE HUMAN MOUTH

OBJECTIVES AND WORK SCOPE

The objective of this research is the development of new or improved techniques of applying cariostatic substances to the mouth that will result in improved access and prolonged retention around caries-prone areas and the evaluation of the reliability and validity of techniques used to assess the effectiveness of the new procedures. The methods developed must be shown by chemical or other means to lead to a significant retention; they must be non-toxic and suitable for use in the human mouth; they must be inexpensive and possible to produce on a large scale; and they must be easily applied and in a form that ultimately can be made available to the general public.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52449-01
ORGANIZATION	UNIVERSITY OF CONNECTICUT HEALTH CENTER
ADDRESS	FARMINGTON CT
INITIAL START DATE	04-01-75
EXPIRATION DATE	03-31-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DOHERTY, NEVILLE
NIDR PROJECT OFFICER	HOROWITZ, HERSCHEL S
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

CLINICAL FIELD TRIAL TO ASSESS COST EFFECT OF CARIES PREVENT AGENTS

OBJECTIVES AND WORK SCOPE

Conduct a clinical field trial consisting of one control and seven treatment groups wherin the cost and clinical effectiveness of each of the following agents and procedures shall be assessed singly and in combination: Supervised topical fluoride applications; applications of bis-GMA pit and fissure sealants; and supervised mouthrinsing program with a fluoride solution.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52450-00
ORGANIZATION	OHIO STATE UNIVERSITY RESEARCH FOUNDATION
ADDRESS	COLUMBUS OH
INITIAL START DATE	06-01-75
EXPIRATION DATE	05-31-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	ROSEN, SAMUEL
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

STUDY ON EFFICACY OF ENZYME - FREE ANTIGENS IN ANTI-CARIES VACCINES

OBJECTIVES AND WORK SCOPE

The Contractor will investigate the effects of specifically induced salivary antibody to whole cells, cell walls, extracts and glucans of Streptococcus mutans upon dental caries in rats.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52451-00
ORGANIZATION	OHIO STATE UNIVERSITY RESEARCH FOUNDATION
ADDRESS	COLUMBUS OH
INITIAL START DATE	06-01-75
EXPIRATION DATE	05-31-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	ROSEN, SAMUEL
NIDR PROJECT OFFICER	ROUSSOS, GERASSIMOS
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

STUDY - BIOCHEMICAL, ENZYMATIC & MICROBIOLOGICAL COMPOSITION OF PLAQUE

OBJECTIVES AND WORK SCOPE

From a population of 275 first graders collect plaque at 3 month intervals. In the plaque determine level of protein, hexose, ketohexose, calcium, phosphorous magnesium, fluoride. Determine presence of Strep. mutans, Strep. sanguis and Strep. Miteor. Also determine level of invertase, glucosyl transerase, dextranase, deaminase, decarboxylases, ammonia and free amino acids.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52452-00
ORGANIZATION	EMORY UNIVERSITY
ADDRESS	ATLANTA GA
INITIAL START DATE	05-21-75
EXPIRATION DATE	05-20-76
ORGANIZATION CODE	INT
PROJECT DIRECTOR	MC CLURE, HAROLD M
NIDR PROJECT OFFICER	KING, C T G
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

INDUCTION ORAL FACIAL MALFORMATIONS IN M RHESUS MONKEY

OBJECTIVES AND WORK SCOPE

The Contractor will conduct investigations pertaining to experimental induction of oral facial malformations in fetal rhesus monkeys; documentation of metabolism of administered drugs in pregnant animals and their fetuses; and chromosomal evaluation of pregnant animals and products of conception, following drug administration. He will establish a breeding colony of rhesus monkeys sufficient to provide 15 pregnancies; establish the menstrual cycles of the females and conduct a breeding program to insure a minimum of 15 timed pregnancies; administer specified compounds to the pregnant animals at various stages of gestation; and monitor effects of drug administration in both pregnant animals and their progeny.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52453-00
ORGANIZATION	UNIVERSITY OF PENNSYLVANIA
ADDRESS	PHILADELPHIA PA
INITIAL START DATE	06-27-75
EXPIRATION DATE	06-26-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	MYERS, HOWARD M
NIDR PROJECT OFFICER	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

IMMUNE STATUS OF PATIENTS WITH SEVERE PERIODONTAL DISEASE

OBJECTIVES AND WORK SCOPE

The Contractor proposes to characterize in detail humoral and cellular immune responses as well as inflammatory response of patients with severe periodontal disease. The study population will consist of forth patients with unusually generalized destructive periodontal disease. Patients in the study group will have no other known medical condition. A suitable age and sex matched control group of equal number shall be included in the study. The immunological status of the patients with severe generalized periodontal disease is to be compared with that of the control group.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52454-00
ORGANIZATION	UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER
ADDRESS	HOUSTON TX
INITIAL START DATE	06-27-75
EXPIRATION DATE	06-26-78
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	LEVY, BARNET M
NIDR PROJECT OFFICER	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

STUDY OF PERIO DISEASE ON PATIENTS WITH ABNORMALITIES OF THE IMMUNE

OBJECTIVES AND WORK SCOPE

The contractor proposes to study a minimum of 25 patients with known deficiencies of the immune system and their state of periodontal health shall be documented to determine if there is any correlation between these two phenomena. The contractor will characterize in detail the immune deficiencies through assay of cellular immune reponse, as well as inflammatory response, and to characterize the clinical periodontal disease entity according to currently acceptable periodontal disease indices.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52455-00
ORGANIZATION	UNIVERSITY OF OREGON HEALTH SCIENCE CENTER
ADDRESS	PORTLAND OR
INITIAL START DATE	06-27-75
EXPIRATION DATE	06-26-78
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	CREAMER, HOWARD R
NIDR PROJECT OFFICER	KAKEHASHI, SAMUEL
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

STUDY OF PERIO DISEASE ON PATIENTS WITH ABNORMALITIES OF THE IMMUNE

OBJECTIVES AND WORK SCOPE

The contractor proposes to study a minimum of 25 patients with known deficiencies of the immune system and their state of periodontal health shall be documented to determine if there is any correlation between these two phenomena. The contractor will characterize in detail the immune deficiencies through assay of cellular immune reponse, as well as inflammatory response, and to characterize the clinical periodontal disease entity according to currently acceptable periodontal disease indices.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52456-00
ORGANIZATION	UNIVERSITY OF ALABAMA IN BIRMINGHAM
ADDRESS	BIRMINGHAM AL
INITIAL START DATE	06-20-75
EXPIRATION DATE	06-19-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	MC GHEE, JERRY R
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

ROLE OF SALIVARY IMMUNOGLOBULIN A DEFICIENCY IN HUMANS RELATE TO CARIES

OBJECTIVES AND WORK SCOPE

The Contractor proposes to study a population of more than 25 IgA deficient patients and appropriate controls to correlate the presence or absence of IgA and caries incidence. He will measure salivary immunoglobulins and factors such as lysozyme, lactoferrin, and peroxidase. Plaque will be collected and analyzed for the principal oral bacteria present. Plaque proteins will be studied from the standpoint of in sutu function-possible coating and/or aggregation of important plaque bacteria. He will correlate these findings with the clinical picture occurring in these patients, including past and present caries, and gingival and Periodontal Disease indices.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52458-00
ORGANIZATION	HAZELTON LABORATORIES
ADDRESS	VIENNA VA
INITIAL START DATE	06-27-75
EXPIRATION DATE	06-26-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DALGARD, DAN W
NIDR PROJECT OFFICER	BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

DEVELOPMENT OF A NON-HUMAN PRIMATE MODEL

OBJECTIVES AND WORK SCOPE

The Contractor proposes to develop an animal model for the study of dental caries in the new world species, namely, the Saimirc scireus species. Emphasis will be placed on designing a method which will induce caries rapidly and yet one in which the results will be applicable to the human disease. In addition to studying caries susceptibility in the feral-reared imported animal, breeding groups will be established to enable studies in the domestically reared infants.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52459-00
ORGANIZATION	UNIV OF CONNECTICUT HEALTH CENTER
ADDRESS	FARMINGTON CT
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BAILIT, HOWARD L
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52460-00
ORGANIZATION	RESEARCH FOUNDATION OF STATE UNIV OF NEW YORK
ADDRESS	ALBANY NY
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	RIPA, LOUIS W
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52461-01
ORGANIZATION	FORSYTH DENTAL CENTER
ADDRESS	BOSTON MA
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DE PAOLA, PAUL F
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52462-01
ORGANIZATION	EASTMAN DENTAL CENTER
ADDRESS	ROCHESTER NY
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	LEVERETT, DENNIS H
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52463-01
ORGANIZATION	UNIVERSITY OF ALABAMA IN BIRMINGHAM
ADDRESS	BIRMINGHAM AL
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	THOMAS, JOE P
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52465-00
ORGANIZATION	STATE OF WISCONSIN
ADDRESS	MADISON WI
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DOHERTY, JOSEPH M
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52466-00
ORGANIZATION	STATE OF MICHIGAN
ADDRESS	LANSING MI
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	SZWEJDA, LOUIS F
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52467-01
ORGANIZATION	MONTANA STATE DEPARTMENT OF HEALTH
ADDRESS	HELENA MT
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	TERRILL, JACK A
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52468-01
ORGANIZATION	VIRGINIA COMMONWEALTH UNIVERSITY
ADDRESS	RICHMOND VA
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	FISHMAN, SHERWIN R
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52469-00
ORGANIZATION	INDEPENDENCE NEIGHBORHOOD COUNCIL U.M.K.C.
ADDRESS	INDEPENDENCE MO
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	SCHAEFER, ROY H
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52470-01
ORGANIZATION	UNIVERSITY OF CALIFORNIA
ADDRESS	SAN FRANCISCO CA
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	SILVERSTEIN, STEVEN
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52471-01
ORGANIZATION	UNIV OF TEXAS HEALTH SCIENCE CENTER
ADDRESS	HOUSTON TX
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	FRIEDMAN, LAWRENCE A
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

COZMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52472-00
ORGANIZATION	COLORADO DEPARTMENT OF HEALTH
ADDRESS	DENVER CO
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	REGER, ROY H
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with a 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explorer. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52473-01
ORGANIZATION	RESEARCH FOR HEALTH IN ERIE COUNTY INC.
ADDRESS	BUFFALO NY
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BISSELL, G. DONALD
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECT

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52474-00
ORGANIZATION	GEAGUA COUNTY HEALTH DEPARTMENT
ADDRESS	CHARDON OH
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	HULL, TERRY E
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52475-00
ORGANIZATION	PRESIDENT AND FELLOWS OF HARVARD COLLEGE
ADDRESS	BOSTON MA
INITIAL START DATE	06-30-75
EXPIRATION DATE	02-28-79
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	DOGON, I. LEON
NIDR PROJECT OFFICER	MILLER, ANN
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

COMMUNITY CARIES PREVENTION DEMONSTRATION PROJECTS

OBJECTIVES AND WORK SCOPE

Briefly, the Contractor shall establish and conduct a school based caries prevention demonstration program; collect and report data on the cost and effectiveness of the program; and develop plans for continuation of the program after the expiration of Federal support. The preventive regimen shall consist of weekly fluoride mouthrinsing with 0.2% solution of sodium fluoride. Grades K-6 or K-8 will be treated. If K-6 are treated, K-9 will be examined each year. If K-8 are treated, K-11 will be examined. DMF tooth and surface data shall be determined with mirror and explore. Radiographs will not be used. Costs and staff time for implementing and conducting the project will be recorded. The Contractor shall also exert every effort to obtain funding from the community for continuation of the project for a period of three years after the Federal support has terminated.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52476-00
ORGANIZATION	TUFTS UNIV SCHOOL OF DENTAL MEDICINE
ADDRESS	BOSTON MA
INITIAL START DATE	06-27-75
EXPIRATION DATE	06-26-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	WHITE, GEORGE E
NIDR PROJECT OFFICER	FREW, RALPH A
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

DEVELOPMENT & EVAL OF A DIAGNOSTIC SYSTEM FOR EARLY DETECTION CARIES

OBJECTIVES AND WORK SCOPE

"The Development and Evaluation of a Diagnostic System for the Early Detection of Dental Caries". This is a research and development of a valid clinical method for diagnosing early carious lesions in human teeth. This method will rely on clinical trials for its final evaluation with comparison made on the basis of caries development between groups differentially exposed to the test agent or procedure.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52477-00
ORGANIZATION	UNIV OF CONNECTICUT
ADDRESS	FARMINGTON CT
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	INT
PROJECT DIRECTOR	FREER, RICHARD J
NIDR PROJECT OFFICER	SCHIFFMANN, ELLIOTT
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

EVAL OF SMALL SYNTHETIC PEPTIDES AS CHEMOATTRACTANTS FOR LEUCOCYTES

OBJECTIVES AND WORK SCOPE

"Evaluation of Small Synthetic Peptides as Chemoattractants for Leucocytes and their Application to Periodontal Disease." This study will provide for the synthesis of 20 or more formylmethionyl peptides or related compounds per year. The synthetic procedure shall involve well-developed methods with few side reactions. The purification of the compounds should be accomplished with simple recrystallization and ion-exchange methods. The compounds then should be tested for chemotactic activity, effects of increasing molecular size, presence or absence of N-acylation, esterification or amidation of carboxyl groups.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52478-00
ORGANIZATION	UNIVERSITY OF MICHIGAN
ADDRESS	ANN ARBOR MI
INITIAL START DATE	06-23-75
EXPIRATION DATE	06-22-76
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	MC NAMARA, JAMES A
NIDR PROJECT OFFICER	CHRISTIANSEN, R L
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

MUSCLE REATTACHMENT AND MIGRATION WITH OR WITHOUT OSSEOUS SURGERY

OBJECTIVES AND WORK SCOPE

This project will provide for studies to determine changes in neuromuscular physiology and craniofacial function due to muscle reattachment, transplantation, and migration with or without osseous surgery, utilizing a young adult primate animal model system to identify and describe stages in muscle adaptation in two types of surgical procedures designed by the Contractor.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52480-00
ORGANIZATION	UNIVERSITY OF PUERTO RICO
ADDRESS	SAN JUAN
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	OQUENDO, FRANCISCO H
NIDR PROJECT OFFICER	MEYERS, RHEA
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

COST BENEFIT STUDY FOR DELIVERY CARIES PREVENTIVE AGENTS & TECHNIQUES

OBJECTIVES AND WORK SCOPE

This project is a study of the cost, feasibility, and effectiveness of training preventive dentistry aides for the delivery of caries preventive agents and techniques. The objectives of the study are: the development and evaluation of a training curriculum and short-term training of six preventive dentistry aides during the first year; and determination of the costs, feasibility, and effectiveness in reducing caries incidence in children, utilizing these trained individuals in a subsequent three-year, school-based caries-preventive program.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52481-00
ORGANIZATION	RESEARCH FOUNDATION OF SUNY
ADDRESS	ALBANY NY
INITIAL START DATE	06-30-75
EXPIRATION DATE	06-29-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	NISENGARD, RUSSEL J
NIDR PROJECT OFFICER	IKARI, NORMAN S
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

IMMUNOLOGIC CROSS-REACTIVITY OF ANTIGENS FROM NON-STREPTOCCAL ORAL

OBJECTIVES AND WORK SCOPE

This research study will provide for the immunologic cross-reactivity of antigens from non-streptococcal oral microorganisms with mammalian tissue and tissue components. This study will further explore preliminary observations that antigenic cross-reactivity between some oral microorganisms and mammalian tissue exists.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52483-00
ORGANIZATION	MEDICAL COLLEGE OF GEORGIA
ADDRESS	AUGUSTA GA
INITIAL START DATE	06-27-75
EXPIRATION DATE	06-26-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BURNETT, GEORGE
NIDR PROJECT OFFICER	SHERN, ROALD J
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

SCREENING OF INDUSTRIALLY CONTROLLED ANTIPLAQUE AGENTS

OBJECTIVES AND WORK SCOPE

Clinical screening of industrially controlled agents for anti-plaque activity; and of food additives and other nonpatent agents for anti-caries activity. Specific screening includes: Bacterial inhibition or minimal inhibitory concentration; glycolysis inhibition; antiaggregation; dissolution and adsoprtion test; animal testing.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	N01 DE52484-00
ORGANIZATION	UNIVERSITY OF PENNSYLVANIA
ADDRESS	PHILADELPHIA PA
INITIAL START DATE	06-27-75
EXPIRATION DATE	06-26-76
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	YANKELL, SAMUEL L
NIDR PROJECT OFFICER	SHERN, ROALD J
NIDR CONTRACT SPECIALIST	KEEFER, DAVID

TITLE:

CLINICAL SCREENING OF ANTIPLAQUE AND ANTIMICROBIAL AGENTS

OBJECTIVES AND WORK SCOPE

Clinical testing of potential antiplaque and antimicrobial agents. Agents shall be applied both singly and in combination in vehicles such as mouthrinses and gels in various regimens and durations. Test groups shall not consist of more than 50 subjects. All testing shell be short term, i.e. 1-16 weeks. CORE MEASUREMENTS plaques extent; dry weight, ph; microflora, gingivitis. ELECTIVE MEASUREMENTS thickness; biochemistry; cervicular flow photography, pO.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	Y01 DE20005
ORGANIZATION	INDIAN HEALTH SERVICE, HSMHA
ADDRESS	ROCKVILLE MD
INITIAL START DATE	10-01-71
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	BUTTS, JOHN
NIDR PROJECT OFFICER	THOMSON, L ARIEL
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

CLINICAL CONTROL OF SMOOTH SURFACE, PIT & FISSURE CARIES

OBJECTIVES AND WORK SCOPE:
Purpose of Project is to determine the dental caries preventive benefit of a combined program of tooth sealant and repeated fluoride application.

Two groups of American Irdian 5th and 6th graders will be randomly assigned to receive maintenance care or preventive measures with maintenance care. Both groups will have all accumulated carious lesions restored before the study commences and receive additional care as required. The Public Health significance of the preventive measures will be determined by contrasting the care required during a three year observation period to estimate the cost benefit.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	Y01 DE30010
ORGANIZATION	NATIONAL BUREAU OF STANDARDS
ADDRESS	WASHINGTON DC
INITIAL START DATE	09-01-72
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	INT
PROJECT DIRECTOR	FRANKLIN, ALAN D
NIDR PROJECT OFFICER	FOWLER, BRUCE O
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

MASS TRANSPORT & PHYSICAL PROPERTIES OF CALCIUM APATITES

OBJECTIVES AND WORK SCOPE:

Prepare and furnish to NIDR large single crystals of pure hydroxyapatite, $Ca_5(PO_4)_3OH$. These crystals are to be prepared from fluorapatite using electrochemical techniques to be developed by the Bureau. They are to be approximately one millimeter thick in the crystallographic c - axis direction and have lateral dimensions in both crystallographic a - axis directions of the order of a centimeter.

Contingent upon satisfactory preparation of pure crystals, the Bureau shall determine the OH^- diffusion coefficients, the ionic conductivity, and the OH^- transference numbers of hydroxyapatite as a function of temperature and crystallographic direction.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	Y01 DE30011
ORGANIZATION	CENTER FOR DISEASE CONTROL, HSMHA
ADDRESS	ATLANTA GA
INITIAL START DATE	11-01-72
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	CHERRY, WILLIAM B
NIDR PROJECT OFFICER	THOMSON, L ARIEL
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

DEVELOPMENT OF SPECIFIC FLUORESCENT ANTIBODY REAGENTS

OBJECTIVFS AND WORK SCOPE:
CDC shall provide the personnel, equipment, and expendable supplies to conduct a research project to: (1) develop, evaluate, and improve to "reagent quality" FA conjugates designed to be specific for certain plaque organisms considered important in dental caries etiology (e.g., Streptococcus mutans, serotypes a-e); (2) research improved methods for preparing reagent conjugates specific for plaque organisms; and (3) determine and recommend optimal conditions for the utilization of FA conjugates in identifying plaque bacteria.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	Y01 DE30012
ORGANIZATION	CENTER FOR DISEASE CONTROL, HSMHA
ADDRESS	ATLANTA GA
INITIAL START DATE	11-01-72
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	KAPLAN, WILLIAM
NIDR PROJECT OFFICER	HAGEAGE, GEORGE J
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

FLUORESCENT ANTIBODY REAGENTS FOR FILAMENTOUS ORGANISMS

OBJECTIVES AND WORK SCOPE:

CDC shall provide the personnel, equipment, and expendable supplies to conduct a research project to: (1) develop and evaluate specific FA conjugates for A. viscosus serotypes 1 and 2, A. naeslundii serotype 2, A. odontolyticus, Arachnia propionica serotypes 1 and 2, and Rothia dentocariosa; (2) define the optimal conditions for the application of these conjugates; and (3) formulate protocols to be followed for the large-scale production of the approved conjugates.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	Y01 DE40014
ORGANIZATION	VETERANS ADMINISTRATION HOSPITAL
ADDRESS	EAST ORANGE NJ
INITIAL START DATE	01-01-74
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	MASHBERG, ARTHUR
NIDR PROJECT OFFICER	HAYES, RICHARD L
NIDR CONTRACT SPECIALIST	BLEVINS, MARION

TITLE:

TECHNIQUES FOR EARLY DETECTION OF ORAL CARCINOMA

OBJECTIVES AND WORK SCOPE:

A study to develop and evaluate clinical criteria for the early detection of oral carcinoma and to evaluate toluidine blue and a DNA-acridine binding test as techniques for detection of clinically inapparent carcinoma and as techniques for identifying patients with precancerous field alterations of the oral mucosa.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	Y01 DE40015
ORGANIZATION	NATIONAL BUREAU OF STANDARDS
ADDRESS	WASHINGTON DC
INITIAL START DATE	07-01-73
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	EXP
PROJECT DIRECTOR	CASSEL, JAMES M
NIDR PROJECT OFFICER	VALEGA, THOMAS M
NIDR CONTRACT SPECIALIST	MULLEN, EDITH

TITLE:

INTERACTIONS OF ORAL STRUCTURES & RESTORATIVE MATERIALS

OBJECTIVES AND WORK SCOPE:

The study is being performed to obtain new knowledge on the properties and interactions of oral structures and restorative materials. The subject matter to be explored and studied, including subtasks, is as follows:

1. Adhesion of Restorative and Caries-Preventive Materials to Tooth Surfaces
   - A. Surface Characterization of Dental Materials by Water Adsorption
   - B. Novel Approach to Development and Assessment of Adhesion in Dental Materials
   - C. Synthesis for Improved Adhesion and Stability of Composite Restorative and Sealant Materials
   - D. Polymer Grafting, a Technique for Bonding to Mineralized Collagen Surfaces

2. Physical, Mechanical and Physicochemical Properties of Hard and Soft Tissues of Dental Materials
   - A. Dimensional Changes in Tooth Structure
   - B. Wear-Resistance of Dental Restorative Materials
   - C. Zinc-Polycarboxylate Dental Cement, Properties and Technique for Improvement

SALIENT RESULTS TO DATE:

In general, it was found that the thermal expansion phenomena in bone are similar to those of dentin. The significance of these studies is to relate the dimensional changes of restorative materials to those of the tooth. A device has been designed and fabricated for measuring accurately the degree of wear to be expedted from composites and other restorative materials, withou the need for long term clinical observation. It was found that the compressive strength of composite carboxylate cements containing potassium titanate as a reinforcing agent is doubled, and tensile strength increased 2 1/2 times. Improved interfacial bonding between fillers and matrices may provide better dental cements than are now available.

COLLABORATIVE RESEARCH PROJECTS

IDENTIFICATION NUMBER	Y01 DE50017
ORGANIZATION	UNITED STATES DEPARTMENT OF THE INTERIOR
ADDRESS	DENVER CO
INITIAL START DATE	04-22-75
EXPIRATION DATE	06-30-75
ORGANIZATION CODE	NCP
PROJECT DIRECTOR	
NIDR PROJECT OFFICER	BOWEN, WILLIAM H
NIDR CONTRACT SPECIALIST	GREENE, JEAN

TITLE:

WATER ANALYSIS FROM FOUR SITES IN COLUMBIA, SOUTH AMERICA

OBJECTIVES AND WORK SCOPE

Specifically, the Contractor will carry out a comprehensive analysis on 3 samples of water from each of 4 sites in Colombia, South America. These samples will be analyzed to determine the total load of chemical constituents ingested.

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